CORRELATION OF MAGNETIC RESONANCE IMAGING FINDINGS WITH MIB-1 LABELING INDEX FOR INTRACRANIAL MENINGIOMAS

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DEPARTMENT OF NEUROLOGICAL SCIENCES
CHRISTIAN MEDICAL COLLEGE
VELLORE

CERTIFICATE

This is to certify that the dissertation titled "Correlation of Magnetic Resonance Imaging Findings with MIB-1 Labeling Index for Intracranial Meningiomas" is the bonafide original work of Dr. Vineesh K. Varghese, submitted in partial fulfillment of the rules and regulations, for Branch-II M.Ch. Neurosurgery, Part-III examination of the Tamil Nadu Dr. M.G.R. Medical University to be held in August 2009.

Signature of the Guides

Dr.Geeta Chacko	Dr. Ari G. Chacko	Dr. Vedantam Rajshekhar
Professor of Neuropathology	Professor of Neurosurgery	Professor of Neurosurgery

Department of Neurological Sciences, Christian Medical College, Vellore.

Introduction

Meningiomas are the most common benign intracranial tumors accounting for 13-26% of all primary intracranial tumors.[1] Meningiomas often recur after seemingly complete removal, although they are benign, generally slow growing and apparently well circumscribed. Recurrence has been estimated to occur in 9 to 15% of benign meningiomas within 10 years after total removal. [2] Atypical and anaplastic meningiomas reportedly have higher recurrence rates (38% and 78% respectively). [2] Recurrences have been attributed to incomplete tumor removal and histological aggressiveness of the tumor. The WHO Type II or Type III meningiomas are thought to recur because these invade the normal surrounding tissues and microscopic remnants of tumor cells that may be inadvertently left behind at surgery grow rapidly. Therefore it is essential that wide resection of dura around the site of tumor attachment is done. Extensive excision may leave a large dural defect, requiring dural grafting, and more importantly may cause neurological deficits depending on the tumor location and size. Therefore preoperative identification of high-risk groups in terms of biological behavior of meningiomas would be useful. A few studies in the past [3] have tried to predict the proliferating potential of meningiomas based on their preoperative MRI findings and three parameters namely, peritumoral brain edema, tumor-brain interface and shape of the tumor had shown a correlation with MIB-1LI of the tumor.

The present study was an attempt to correlate the above mentioned MRI characteristics with the MIB-1LI of the tumor, to see if a preoperative prediction of biological behavior of meningiomas was possible.

Literature Review

History

Cushing and Eisenhardt [4] in their famous monograph on meningiomas stated that meningiomas have left their unmistakable traces even on prehistoric skulls. This was the most accepted terminology after a series of names these tumors were designated with. One of the first recorded names for this tumor is in Chapter XXI of a book written by Louis in 18th century where he calls these tumors *Fungus Durae Matris.* Richard Bright in "Reports of Medical Cases" (1831) stated that the tumor is a growth from the dura mater or rather from the arachnoid lining the dura matter. Cruveilhier in his 'Anatomie Pathologique" 1835 termed it " *Tumeurs fongueuses*" and " *Tumeurs cancereuses des meninges*" and in 1856 he questioned the acceptance of the tumor as malignant considering the fact that the tumor remained without invading the cerebral tissues for many years. In 1851, Hermann Lebert classified these tumors into those, that were cancerous, and those that were not. He called the non-cancerous ones as "tumeurs fibro-plastiques intracraniennes. In 1854, Sir James Paget in his "Lectures on Surgical Pathology" classified these tumors to be "less malignant than cancer". Robert Virchow called these tumors 'psammomomas' based on the post mortem observation of "brain sand" accumulations in these tumors. Ludwig Meyer, Bouchard and Robin in 1859 substituted the name "epithelioma" considering that they arose from serous surfaces including arachnoid. In 1864 John Cleland described two tumors, which he had encountered in the dissecting room, one of them having arisen from the olfactory groove and the other from the right frontal region. Microscopically, these tumors were found to be rich in cellular concretions. They were found to be well separated from the dura mater and were named "villous tumors of the arachnoid" In 1865, with the renaming of the lining membranes as "endothelium", Camillo Golgi suggested the term 'endothelioma' for these tumors.

Subsequently Kolliker called them “mesothelioma” around 1882 when the lining membranes had been named as Mesothelium. The word meningioma came to usage for the first time in 1922 by Harvey Cushing.

These tumors arise from the arachnoid cap cells, which are specialized clump of arachnoid cells that are exposed to the venous blood of dural venous sinus.[5] The latest name for the cells of origin for meningioma is meningothelial cell. Meningiomas are generally seen as tumors attached to the dura and compressing the underlying brain. They may also occur as a flattened sheath of tumor taking the shape of the underlying bone, so called the en plaque meningioma. Rarely, they may arise in a location where dural attachment cannot be demonstrated (e.g. intraventricular)

Site of origin

Meningiomas can arise from the dura at any site, but most commonly arise from the skull vault, skull base (the planum sphenoidale, the sphenoid wing, the petrous ridge, the cavernous sinus and perisellar region and the clivus) and at sites of dural reflections (falx cerebri, tentorium cerebelli and dura of the adjacent venous sinuses). [6] Other less common intracranial sites of origin including the optic-nerve sheath and the choroid plexus (intraventricular meningioma). 10% of meningiomas arise in the spine. The distribution of meningiomas as seen in Cushing’s series is shown in **Table 1**. Very rarely, meningiomas have also arisen wholly outside the cranio-spinal axis, in the ear and temporal bone, mandible, foot, mediastinum, and lung. [6]

Multiple Meningiomas

Multiple meningiomas are defined as two or more meningiomas appearing simultaneously or sequentially in the same patient. [7] Multiple meningiomas and familial types are rare and mostly associated with neurofibromatosis type 2.

Etiology

Trauma, radiation, oncogenic viruses and genetic alterations in the long arm of chromosome 22 have been implicated in the etiology of meningiomas.[5] In children who have received prophylactic irradiation for acute lymphoblastic leukaemia, the incidence of intracranial tumours is ten times higher than in the general population (median time to onset 7 years) but only 10% of these tumours are meningiomas. [6]

Macroscopy

Meningiomas are rubbery or firm, well-demarcated, sometimes lobulated, rounded masses that have a broad dural attachment. They can invade through dura to involve the skull where they induce characteristic hyperostosis, even when they are benign. [8] They may infiltrate skin and extend to extracranial compartments such as the orbit when malignant. They are adherent to, or encase arterial walls, seldom infiltrating them, however, invasion into nearby dural venous sinuses is quite common. [1]

About 1-10% of meningiomas undergo cystic changes [9, 10] Pathologically, macroscopic cyst formation tends to occur most often in meningothelial meningiomas during adulthood, whereas the fibroblastic form predominates in infancy [9]

WHO GRADING (Table 2)

In 2007, the World Health Organization revised the classification of Meningiomas. [11] The inclusion of brain invasion as a criterion for atypia is the only significant modification to the 2000 WHO grading scheme. By the likelihood of recurrence and histopathological findings, meningiomas are grouped into three grades.

WHO Grade I

The grade 1 tumors include Meningothelial, Fibroblastic, Transitional, Psammomatous, Angiomatous, Microcystic, Secretory, Lymphoplasmacyte-rich and Metaplastic meningiomas. Grade 1 includes tumor variants that have a low risk of recurrence. [1] The histopathological WHO grade 1 tumors generally follow a benign clinical course and have only occasional mitotic figures, although pleomorphic nuclei do occur. Various architectural patterns are seen within this group. The three commonest architectural patterns are meningothelial, fibroblastic, and transitional [1]

Meningothelial type is the classical variant where the cells form lobules surrounded by thin collagenous septae. The tumor cells resemble those of normal arachnoid with oval nuclei.

In the fibroblastic type spindle shaped cells resembling fibroblasts form parallel and interlacing bundles on a matrix abundant in collagen and reticulin.

The characteristic histological features of cellular whorls and psammoma bodies (round calcified bodies) are seen most commonly in the transitional variant. [6]

Psammomatous meningiomas contain large numbers of psammoma bodies. Angiomatous meningiomas are highly vascular. When a small portion of the tumor is histologically studied, this variant can be confused with capillary hemangioblastoma or even a vascular

malformation.[1] The Microcystic variant has cells with elongated processes and a loose mucinous background, giving an appearance of small cysts. The hallmark of the secretory subtype is the presence of focal epithelial differentiation with lumina containing an eosinophilic material. These structures are called pseudopsammoma bodies and stain positive with carcinoembryonic antigen (CEA). The Lymphoplasmocytic variant has extensive chronic inflammatory infilterates with a meningiothelial-like picture in the background. The Metaplastic type is a benign meningioma with focal mesenchymal differentiation.

WHO Grade II

Atypical meningiomas are defined as those tumors with increased mitotic activity (four or more mitoses per ten high power fields) or three or more of the following five features: 1) increased cellularity, 2) small cells with high nuclear/cytoplasmic ratio, 3) prominent nucleoli, 4) uninterrupted patternless or sheet like growth and 5) foci of spontaneous or geographic necrosis [1] **(Table 3)** Two subtypes of WHO grade II meningiomas are recognized on the basis of their architectural pattern: Clear-cell and Chordoid meningiomas.

WHO Grade III

Grade III meningiomas are subclassified on the basis of their architectural pattern into papillary and rhabdoid subtypes. **(Table 2)** Papillary meningiomas are rare variants and are mostly seen in children. They are defined by a perivascular pseudopapillary pattern. Rhabdoid meningiomas contain rhabdoid cells that have a specific microscopic appearance with eccentric nuclei, abundant globular eosinophilic cytoplasm, and paranuclear inclusions. Anaplastic (malignant) meningiomas have obvious malignant cytology, a high mitotic rate (20 or more mitotic figures in ten high-power fields), or both. These tumours show a high frequency of local and brain invasion, recurrence and metastases. [11]

Brain invasion is defined histologically as islands of neoplastic cells that have invaded through the pia to involve underlying cortical tissue, commonly producing a gliotic reaction. Brain invasion is now one of the criteria used for grading tumours in the WHO 2007 classification, [11] because brain invasion is associated with subtotal resection and a higher rate of recurrence.

Recurrence rates

Atypical and anaplastic meningiomas reportedly have higher incidence of recurrence rates, 38% and 78% respectively, within 5 years after complete surgical removal, compared to 3 %- 7 % recurrence rates seen for typical meningiomas in old literature. [2] The 5-year rate for recurrence of symptoms (regardless of the method of treatment) was 18.2% for those with benign tumors and 27.5% for those with malignant tumors. [12] Recurrence rates were 14.8% for benign meningiomas, 66.7% for atypical meningiomas and 100% for malignant meningiomas according to study by Tyagi et al. [13]

Simpson in 1957, [61] classified rate of recurrence based on extent of tumor resection. Simpson's Grade I removal is macroscopically complete, with excision of the dural attachment of the tumor and any abnormal bone. Grade II is the macroscopically complete removal of the tumor and its visible extensions, with coagulation of its dural attachment. Grade III is the macroscopically complete removal of the intradural tumor without resection or coagulation of its dural attachment or extradural extensions. Grade IV is a partial removal of the tumor, leaving the intradural portion of the tumor in place. Grade V is simple decompression of the tumor with or without a biopsy.

In Simpson`s series of 265 meningiomas, he recorded an overall recurrence rate of 21%. The recurrence rates were 9% for grade I excision, 19% following grade II excision, 29%

following grade III excision and 44% following grade IV excision. Based on Simpson`s Grading, subsequent studies have shown similar rates of recurrence, depending on the extent of surgical resection. Mohammed et al [62] who followed up 25 cases of meningiomas for a period of 10 years found the recurrence rates to be 8% following grade I excision, 15% following grade II and grade III excisions, 29% recurrence following grade IV and 33% following grade V excision. Chan et al [10] found the recurrence rates to be 11% for grade I, 22% for grade II, 28% for grade III, 33% following grade IV excision and a 100% recurrence rate following grade V excision. These studies proved that the extent of tumor resection was the single most important factor associated with tumor recurrence and that the extent of excision in turn depended on the location of tumor. The convexity tumors had higher rates of complete resection in comparison to skull base tumors.

Growth Potential of Meningiomas as assessed by various labeling indices

The growth potential of meningiomas is variable, some remain unchanged in size for a long time, whereas others grow rapidly. [14]

Bromodeoxyuridine

Bromodeoxyuridine (BrdU) can detect antigens expressed during the S phase of cell division. Histopathological studies using BrdU labeling index (BrdU LI) require intravenous injection of BrdU prior to surgery or incubation of cultured tumor cells with BrdU. Several studies have shown that BrdU LI of recurrent tumors was significantly higher than that of the non-recurrent meningiomas. [14, 15] However, it is inappropriate for retrospective studies since it requires intravenous BrdU injection prior to surgery or incubation of cultured cells with BrdU.

Ki-67

The **Ki-67** protein is a marker for cell proliferation. [16] During interphase, the Ki-67 antigen can be exclusively detected within the cell nucleus, whereas in mitosis most of the protein is relocated to the surface of the chromosomes. Ki-67 protein is present during all active phases of the cell cycle (G_1, S, G_2, and mitosis), but is absent from resting cells (G_0). Ki-67 is an excellent marker to determine the growth fraction of a given cell population. Cell kinetic studies using BrdU LI or Ki-67 staining index reliably predict the speed of growth in various tumors. [14, 15] Shibuya et al [17] showed that there was a correlation between Ki-67 and WHO grade of the tumor. They examined 44 benign and 8 malignant meningiomas and reported mean Ki-67 indices to be 1.45% to 7.2% respectively. They also showed a correlation between Ki-67 and bromodeoxyuridine labeling index (BrdU)

MIB-1 LABELING INDEX (MIB-1LI)

MIB-1 (antibody to Ki-67) is believed to be the most reliable marker for proliferation in meningiomas. [6] It reacts with nuclear antigen expressed in the cell cycle of G1, G2 and M phases of cell division.

Correlation with WHO grade: Numerous studies have shown that the MIB-1 LI for atypical and malignant meningiomas are higher than in those without atypia. [18, 19, 20] Abramovich and Prayson [20] in their study of 90 cases of meningiomas reported that the mean MIB-1LIs for the benign, atypical and malignant groups were 1.0% (range, 0 to 5.5%), 5.5% (range, 0.1 to 32.5%) and 12.0% (range, 0.3 to 32.5%) respectively. Differences in the mean MIB-1LI between groups were statistically significant, with p values of <.0001 (benign vs. atypical) and .0012 (atypical vs. malignant). However, the mean MIB-1LIs for recurrent versus nonrecurring tumors were not significantly different [7.1% versus 3.8%] (p=0.32). Their study had 32 recurrent and 27 non recurrent meningiomas. The mean MIB-1LI for patients who were alive with or without tumor was significantly lower (6.2%) compared with those who died (14.2%) and concluded that the mean MIB-1LI discriminated between benign, aggressive and malignant meningiomas. They also concluded that the interpretation of an individual MIB-1LI in a given tumor has to be done with caution, as there was an overlap between MIB-1LI ranges among different groups.

The cut-off for MIB-1LI that has maximum validity in correlation with the histological grade was different according to different authors. Ming-Tak et al, [21] in their prospective study, showed that, 30 of 31 patients (97%) with a MIB-1LI > 10 had recurrence of meningioma in the 10 year follow up period and of this 71% of them recurred within 5 years. Among the 52 patients with MIB-1LI < 10, there was no recurrence was seen in 10 years. The MIB-1LI for

the entire group studied ranged from 0.4 to 33.5 (mean LI, 8.4). They therefore recommend a cut-off of 10 for MIB-1LI to differentiate between benign and atypical meningiomas.

A retrospective study by Devaprasath et al, [22] of all atypical and malignant meningiomas diagnosed at our center between January 1995 and June 2000, showed that the MIB-1LI has the highest validity in the diagnosis of atypia in meningiomas at a threshold level of 7%. Meningiomas with MIB-1LI >7% were found to have statistically significant correlations with an increased mitotic index (>4 / 10 HPF), uninterrupted patternless or sheet-like growth, increased cellularity and small cells with a high nuclear:cytoplasmic ratio, all of which are WHO criteria for the diagnosis of atypia [22]

Age and gender correlates of MIB-1LI

Matsuno et al [23] observed that the mean MIB-1LI for patients less than 40 years of age was 7.5% as compared to 2.9% for patients more than 40 years of age. This was because of a higher incidence of atypical meningiomas in the pediatric population. The recurrence rates for meningiomas were the same as in adult meningiomas. In the same study they also found that the mean MIB-1LI of the 50 male patients with meningioma was 5.5%, whereas that of 77 female patients was 2.7%. These age and sex related differences in MIB-1LI were statistically significant. However, Sandberg et al [24] found that as in adult tumors, higher MIB-1LI correlated with pathological atypia in childhood meningiomas also. They observed a statistically significant difference between the median MIB-1LI for tumors with atypical or malignant features (median, 12.3%; range, 7.0–31.6%) and that for tumors without atypia (median, 7.0%; range, 1.2–12.6%; *P* , 0.02) in children.

In summary, various studies have pointed out a statistically significant correlation between a high MIB-1LI value and the aggressive nature of the meningioma [18, 19, 20] as well as with

higher recurrence rates. [19] There have been studies showing higher incidence of atypical meningiomas and hence a higher range of MIB-1LI values among pediatric age group. [19, 23] The study from our institution showed that a cut-off value of 7% for MIB-1LI had highest validity in diagnosis of atypical meningiomas.[22]

Although the study of proliferation rates is valuable in planning treatment, these can be applied only after surgery. Clinicoradiological findings that help predict the growth potential or biological behavior of meningiomas, before surgical treatment would be beneficial for appropriate planning of surgery and predicting outcomes.

Natural history of incidentally diagnosed meningiomas

Advances in neuroimaging (computed tomography and magnetic resonance imaging) have led to the increased identification of patients with incidental meningiomas. There is little information on the natural history of these tumors, particularly since they are slow growing. It is unclear whether the growth potential increases after the tumor reaches a certain size or whether there is any relationship with the age or sex of the patient or the follow-up time. Nakamura et al [25] in a retrospective review of 41 patients with incidentally detected meningiomas studied the absolute and relative growth rate and tumor doubling time of these tumors without treatment. The diagnosis of meningioma was made on the basis of the radiological appearance of the tumor and growth rates measured on annual or six monthly follow up imaging. Only 6 of their 41 (14.6%) patients recruited symptoms related to the tumor during the study period and had to be operated. They found that, growth rates varied from 0.03 – 2.6 cubic centimeters a year and the majority (66%) had growth rates less than 1 cubic centimeter/year. Annual growth rates tended to be higher and tumor doubling times

shorter in younger patients. They did not find any correlation with the initial tumor size and tumor doubling time. In another study, Niiro et al [26] measured the annual absolute growth rates in 37 patients with asymptomatic meningiomas and found that tumor growth occurred in 14 patients and was associated with age and tumor size. The majority showed no growth in their tumors over a follow up period of 41 months.

Summarizing, the assessment of the exact growth rate of benign brain tumors is difficult, and several different methods for tumor growth measurement have been used. As seen in the above mentioned studies, although the majority (60-65%) of patients with incidental meningiomas show no growth, 30-35% of these tumors do grow and radiological prediction of growth potential may help in counseling these patients an deciding and appropriate management, that is, follow up, surgery or radiosurgery.

Radiology

Plain X-ray of skull

On a plain X-ray of the skull, the changes that are associated with meningiomas are bone erosion, hyperostosis, tumor calcification and expanded paranasal sinuses (seen in certain anterior basal tumors). Presence of calcification is associated with benign meningiomas. [4]

CT scan

Plain and contrast computed tomography detects 85% and 95% of intracranial meningiomas respectively. CT scan usually demonstrates a hypo or isodense mass with intense enhancement with contrast. Plain CT scans show a sharply circumscribed round or smoothly lobulated mass that abutts a dural surface, usually at an obtuse angle, with buckling of the underlying cortex in some cases. Approximately 75% are hyperdense relative to adjacent brain. Intratumoral hemorrhage is uncommon in meningiomas. In a series of 313 meningiomas studied by Cushing and Eisenhardt [4] and 280 meningiomas studied by Horsley and Olivecrona, [4] there were no cases of intratumoral bleed.

CT and Bone involvement

Abnormalities of bone are frequently encountered in meningiomas. Cushing's series had 25% of cases showing hyperostosis.[4] Diagnosis of hyperostosis can be made easily with computerized tomography and magnetic resonance imaging. Different types of bony reactions were encountered in Cushing and Eisenhardt`s series namely, bone destruction, extensive hyperostosis and endostosis, which is a process of abnormal bone formation in which ossification takes place within the cartilage. In the study by Bikmaz et al, [8] on 67 sphenoid wing meningiomas, there were 17 cases with bone hyperostosis and histopathological evaluation of bone specimens in 14 cases, revealed no histological evidence

of malignancy. They had achieved a total removal in 14 cases (82.3%), with only one recurrence (7.1%) over a mean follow-up period of 36 months (range 5–72 months) suggesting that bony changes in meningioma is not indicative of its malignant potential.

Theories of hyperostosis:

The association of hyperostosis with meningiomas was first described by Brissaud and Lereboullet in 1903. [8] Hyperostosis results from skull trauma and the tumor is secondary to irritation of the dura by the bony growth. Slight movements of the sagittal suture and bregma, inducing a stimulatory effect on cells of pachymeninges, explains increased frequency of hyperostosing meningiomas in the parasagittal area. [4] Vasogenic theory states that enhanced circulation in the bone, secondary to presence of meningiomas is responsible for hyperostosis. The other theory for hyperostosis is that tumor cells themselves can produce fibroblasts, osteoblasts and osteoclasts [4]

Summarizing, hyperostosis has not shown to be one of the factors which can predict the aggressive behavior or recurrence rates in meningiomas.

CT and tumor calcification

Calcification is seen in 20-25% of the tumors. [28] Calcification can be focal or diffuse. They can occur in patterns like psammomatous (sand like), sunburst, or globular and even rim like pattern. Presence of calcification is considered a feature of benign meningiomas [29]

MRI findings of meningioma

T1W and T2W images

Regardless of the histological type, most meningiomas are iso- or slightly hypointense relative to cortex on T1 weighted studies, although signal on T2 weighted studies is variable. Elster et al [30] correlated the MRI appearance of 40 biopsy proven meningiomas with

histological pattern. They observed that meningiomas that are markedly hypointense on T2 weighted images were composed predominantly of fibroblastic or transitional elements. Syncytial meningiomas composed of sheets of contiguous cells and rather sparse interstitium had higher signal on T2 weighted images. Angiomatous meningiomas with dilated blood vessels, vacuoles and high cellularity, were also found to be hyperintense on T2 weighted images. [30] This correlation of signal intensity with histologic subtype was highly significant statistically ($P < .001$, in K-W analysis of variance)

Chen et al [31] made similar observations in correlation of T2W images with histological type of the tumor. MRI is also helpful in predicting the dural venous sinus involvement by the tumor. Zee et al [9] showed a 90% positive predictive value in detecting dural venous sinus involvement by meningiomas on T1W images.

FLAIR sequences

In the study by Gasperetto et al [32] on 78 patients with meningiomas, in the FLAIR sequence 69% of tumors had high signal, 22 % had intermediate signal and 9 % had low signal. The lesions were heterogenous on FLAIR sequences in 64% of cases. In a prospective study on 21 patients with meningiomas, Yrjana et al [33] reported that peritumoral edema was most clearly seen in FLAIR images as areas of high signal around the tumor. They studied the correlation between MRI characteristics and various tissue parameters of meningiomas namely consistency, bleeding at surgery, progesterone receptor expression, micro vessel density and collagen content of the tumor. They found a positive correlation between progesterone receptor expression and relative intensity of tumor on FLAIR images. A negative correlation was found between the previously mentioned intensity and grade of collagen content in meningioma tissue. Surgical bleeding and blood loss correlated moderately with relative intensity on FLAIR images. Time to maximum enhancement derived from dynamic T1-weighted imaging predicts microvascular density of meningioma tissue.

They concluded that MR imaging cannot give definitive answers to questions of consistency, vascularity, and histologic parameters of meningiomas but may still give us an idea of the factors that should be taken into account when planning surgery of meningioma.

Contrast

MRI with intravenous gadolinium enhancement provides valuable additional information in the radiological evaluation of meningiomas. Meningiomas show a uniform enhancement on intravenous administration of gadolinium compound (Gd-DTPA). Enhancement pattern in meningiomas may be homogenous or heterogenous. In the study done on MRI findings of 78 patients with meningiomas, by Gasperetto et al [32] following contrast administration, 83% had accentuated enhancement and 17% had moderate enhancement. They also noted that the contrast enhancement was heterogenous in 64% of cases. Dural tail sign was seen in 59% and 29% of the tumors showed evidence of bone infiltration in their study.

Dural tail

In 1989, Wilms [34] first described meningeal enhancement surrounding meningiomas on T1 weighted MRI scans obtained with gadolinium administration. This finding has been described as 'dural tail sign.' or "flare sign". Nakau et al [35] did a pathological study on the dura mater resected from the margins of meningiomas exhibiting the 'flare sign' and tried to assess the optimal width of dura mater that needs to be resected from tumor margin. They demonstrated tumor cells in dural tail, but were not able to point out the exact extent of dural infiltration beyond the tumor margins. They suggested a wide excision of dura mater that exhibited the flare sign.

Consistency

Yamaguchi et al [36] studied the relationship of MRI findings with the **consistency** of the tumor. They found, in their study of 50 cases that there was no significant relationship between the T1W images and the consistency of the tumors. T2W and proton density (PD) images on the other hand had statistically significant relationship with the tumor consistency, revealing soft meningiomas as hyperintense in 80.8% of cases. Hypointensity on T1 with hyperintensity on T2 and PD images always revealed a soft tumor. Isointensity or hypointensity on T2 or PD indicated a hard tumor. If the image findings were suggestive of a `hard` meningioma, a preoperative embolization was considered beneficial to induce necrosis and convert it to a `soft` meningioma, which was easier to excise. [36] Cystic degeneration occurs in meningiomas and these are seen as hypointense lesions in the T1W images.

Chen et al [31] reported a study on 54 patients, where they predicted the gross and microscopic tumor characteristics such as vascularity, consistency, venous sinus involvement, presence of cystic changes and histopathological features using MRI. They showed that hyperintensity on T2W images, was useful in predicting hypervascularity. They also found that soft tumors were hyperintense on T2w images, as was reported in other studies. [30] They did not find any correlation between the peritumoral edema and vascularity or histological type of the tumor.

Vascularity

Previous studies with CT [37] scan had showed no relationship between the degree of contrast enhancement and vascularity of the tumor. Similarly there was no correlation between gadolinium enhancement on MRI and the vascularity or histological type of meningioma.[31] The other observation in the study was that cystic meningiomas were best identified with T1W images. They appear hypointense to gray matter in T1W and hyperintense to gray in T2W images. Flow voids on MRI are seen secondary to pulsatile and turbulent high velocity

blood flow, [31] and are seen on T1W images in the presence of large intratumoral blood vessels. [37]

Summarizing, intracranial meningiomas are generally found to have heterogenous low signal on T1W MR images and heterogenous intensities on T2W and FLAIR images, with intense enhancement following contrast administration. Presence of a low T2W signal suggests a hard tumor consistency probably, due to a high collagen content.

Dural enhancement around the meningioma (dural tail sign) warrants a wider excision of dura mater. MRV helps in pre operative assessment of venous sinus involvement and venous drainage of the tumor.

Peritumoral edema

There have been studies that correlated peritumoral brain edema (PTBE) with various clinico pathological parameters of meningiomas. [28, 31, 36-50]

Etiology of peritumoral edema

The exact etiology of peritumoral brain edema associated with meningiomas is not well understood.[50] Factors that may affect the occurrence of peritumoral edema include tumor size, histological subtypes, vascularity, levels of Vascular Endothelial Growth Factor (VEGF) and sex hormone in the tumor, venous stasis, and brain invasion [42, 13]

Peritumoral edema and Size

Lee et al [47] correlated the volume of the tumor with the volume of the peritumoral edema. The study used edema index described previously [44] and was calculated as follows:

Edema index (EI) = V ($_{edema}$+$_{tumor}$)/V_{tumor}, where V= volume; EI was equal to 1 when edema was absent. The volume of tumor and edema was measured from the MR image. The maximal perpendicular diameters (radii *a* and *b*) of the tumor and the edema in the axial MR

sections were measured. Coronal diameters of the tumor and the edema were approximated by using the number of axial images showing tumor tissue and edema multiplied by the slice thickness. (radius c) The volume was calculated using the formula $V = 4/3\pi abc$.

The Edema Index was higher in the larger tumors presumably because they cause more brain compression, leading to ischemia and secondary brain edema. According to their study, large tumor volume was closely related to increased pial cortical blood supply that is considered to be a critical factor in the development of PTBE. Although some studies noted no correlation between meningioma size and the incidence of peritumoral edema, [48, 49] a number of authors agree that there is a significantly higher incidence of PTBE with large meningiomas in comparison with small ones [44, 45, 51]

Vascular Endothelial Growth Factor and edema

Ding et al [46] examined the protein and gene expression of VEGF in 37 meningiomas and peritumoral brain areas. Immunohistochemical staining and immunoblotting were performed to detect the expression of VEGF protein in the tumor and edema. Reverse-transcriptase polymerase chain reaction (RT-PCR) was used to analyze the presence and quantity of VEGF mRNA. The extent of PTBE was estimated as an edema index (EI) based on preoperative magnetic resonance imaging (similar to the method described by Lee et al. [47] The expression of both protein and mRNA in the tumor had a significant correlation with EI and the mRNA was not seen in areas of perilesional edema, suggesting that VEGF macromolecules are secreted by the tumor tissue and enter peritumoral normal brain tissue to induce edema. They did not correlate the levels of VEGF to the grade of the edema.

Location and proximity to venous sinus

Previous reports on the relationship between tumor location and PTBE have not demonstrated consistent results. Convexity, [31, 49, 50] parasagittal, [49, 50] falx [31] and sphenoid ridge [31] are

sites where tumor produce more PTBE. The reasons for this discrepancy are thought to be differences in the classification of tumor attachment, especially in older research performed using computed tomography and in the evaluation of edema (edema index or EI).[43]

However, several authors agreed that tumors on the tentorium and posterior fossa were associated with less peritumoral edema [49, 50]

Although, some studies on meningiomas have associated edema with proximity to venous sinuses, Bitzer et al, [44] did not find increased edema in the meningiomas that obstructed venous drainage of their total number of 134 tumors.

Correlation of edema with histological grade and histological subtype:

Lee et al [47] studied 79 meningiomas, 71 Grade I and 8 Grade II/III and found a significantly higher incidence of PTBE in the grade II/III group ($p = 0.004$). However, despite being benign the 'Angiomatous' variant had marked PTBE. While the atypical and malignant subtypes correlated with PTBE in the univariate analyses they did not reach significance in the multivariate analyses, when the pial-cortical arterial supply, male sex and hyperintensity on T2WI were the other factors included in the analysis.

Ide et al, [42] found a significant correlation of both the MIB-1LI and tumor size with the extent of edema. They studied MIB-1LI in 57 histologically proven intracranial meningiomas along with radiological factors that could influence development of peritumoral brain edema. Their study had 54 benign and only 2 atypical and 1 anaplastic meningiomas. The extent of peritumoral brain edema was determined using preoperative magnetic resonance imaging and was classified as Grade 0, 1, or 2 in order of increasing severity. Grade 0 represented no brain parenchymal edema or a small halo around the tumor, Grade 1 represented edema extending along white matter tracts for varying distances without involving the entire hemisphere and Grade 2 represented holohemispheric or near-holohemispheric edema. The

MIB-1LIs of the 57 cases ranged from 0.06-6.8% (median, 0.8%). There were 26 grade 0, 20 grade 1, and 11 grade 2 edema cases. The MIB-1LI rose in order of increasing edema severity. There was a statistically significant correlation between the MIB-1LI and the extent of brain edema ($p<0.0001$) and also between the tumor size and the extent of brain edema ($P=0.001$). Atypical/anaplastic meningiomas were associated with peritumoral brain edema more often than any other subtype ($P<0.005$). However, it was not clear as to how a statistical significance was seen, with only two cases of atypical and only one case of anaplastic meningioma in their study Moreover, the MIB-1LI of the two atypical meningiomas were 2.1% and 3.4% and the MIB-1LI of malignant meningioma was 6.68% which was low in comparison with the cut off of 7% used in our study. They also found that the meningothelial subtypes and one transitional meningioma had MIB-1LI higher than the lowest MIB-1LI of the atypical meningiomas, raising doubts regarding the accuracy of these MIB-1LI.

Some studies in the past have linked peritumoral edema with malignancy. [28, 39, 40] On the other hand, there were some other studies like that by Younis et al, [41] where one third of patients with malignant meningiomas, had no cerebral edema, suggesting that the presence of edema does not necessarily indicate a malignant lesion and absence of edema does not necessarily exclude malignancy.

Peritumoral edema association with brain invasion:

Tamiya et al [43] retrospectively studied radiological factors on MRI causing peritumoral edema in 125 meningiomas with 121 benign, no atypical and 4 malignant tumors. The factors studied were histology, tumor size, location, brain-tumor interface, signal intensity on T2-weighted scans, contrast enhancement, and cyst formation, as well as tumor vascularity and blood supply (as observed in digital subtraction angiography studies). They did not do a

MIB-1LI or WHO grading. A relationship between the tumor size and the volume of PTBE (measured using the edema index EI= Volume of tumor+edema/ volume of tumor) was observed. Convexity and middle fossa meningiomas demonstrated the highest mean edema indices. Meningothelial, Anaplastic, Microcystic, and Angiomatous subtypes exhibited higher edema indices than did other types.

Multivariate analysis demonstrated two significant radiological factors: cortical penetration (as defined by the disappearance of the arachnoid layer on magnetic resonance imaging scans) and vascular supply from the pial-cortical arteries as observed on angiograms.

Mantle et al [38] had another grading system for the peritumoral edema for meningiomas, as seen on the non-contrast CT scan. It was expressed as the thickness of the low attenuation area (7-25 Hounsfield units), measured to the nearest centimeter from the outer edge of the tumor to the outer edge of the parenchyma on the best axial slice (that which shows the largest cross sectional area of the tumor). The edema grading scale was validated by correlation with the actual volume of edema determined by digitizing 29 CT scans by using public domain software. The edema volume and tumor volume was calculated in cubic centimeters. According to this study, the chance of brain invasion increased by 20% for each centimeter of edema ($p = 0.0001$; 124 cases). The presence of brain invasion seen on histopathology in 42 cases was predictive of recurrence after complete resection with an accuracy of 83%, a sensitivity of 89%, and a specificity of 82%.

In the study by Fransesco et al, [52] the tumor-brain interface on preoperative CT scans was analyzed and the perifocal effects on brain tissue surrounding meningiomas were classified into three groups: no perifocal reaction, a perifocal halo-like hypodensity, and a hemispheric finger-like hypodensity. Of the 52 patients in the study, 13 had no reaction around the meningioma on the CT scan, 39 had zones of diminished density surrounding the lesions; 21

had halo-like perifocal hypodense areas confined to the vicinities of the tumors. Of these 18 patients showed finger-like hemispheric areas that spread into the white matter.

Summary of peritumoral edema

The exact etiology of peritumoral edema in meningioma is not known, but factors such as size, proximity to sinuses, sex hormone receptors and brain invasion have been implicated. Vascular Endothelial Growth Factor has been shown to be secreted by meningiomas and the degree of its expression has been correlated with the edema grade. The correlation of peritumoral brain edema with WHO grade of the tumor is inconsistent with a few studies correlating higher grades of edema with higher WHO grades. On the contrary severe edema has been seen in certain benign variants as well. Recently Zhang et al [53] showed that the difference in the perfusion MR imaging findings of peritumoral brain edema in benign and malignant tumors, may find its application in predicting the histological grade of the tumor.

Interface between Meningioma and the Brain on MRI

A few studies in the past have studied the tumor-brain interface of meningioma. [41, 52, 54, 55, 56]

Microscopy

Nakasu et al [55] studied the microscopic anatomy of tumor-brain interface of 50 meningiomas and found that the type 4 collagen which was present in the basement membrane forming the demarcation between the tumor and brain of benign meningiomas, was lacking in the atypical and anaplastic variants. In two benign meningiomas that looked like an invasive growth, Col4 staining was seen above the brain and pia mater-like structure covered the tumor surface in both cases. Statistical significance of this finding however was not calculated.

Macroscopy

Nakasu et al [56] in a descriptive study, based on 27 non-operated supratentorial meningiomas from autopsies, classified the tumor-brain interface into four types namely, smooth, lobular, finger-like expansion, and invasive.

Radiology

An indistinct tumor-brain interface on CT and MR imaging may indicate brain invasion and has been associated with aggressiveness of the tumors. [41] Invasion of the brain is difficult to assess radiologically because the invasion may be just microscopic. The signal intensities from the tumor are sometimes very similar to brain tissue; thereby the tumor-brain interface may be difficult to interpret. This difficulty can be overcome by administrating intravenous contrast. [55]

Nakasu, et al [55] studied the MRI findings of the tumor-brain interface. The thick collagenous connective tissue, which was seen around four tumors, was shown as a low signal intensity rim on both T1 and T2-weighted images. A rim of low signal intensity on a T1-weighted image and high signal intensity on a T2-weighted image most likely represented a cerebrospinal fluid space: this finding was seen around eight tumors. No distinct rim could be identified in five tumors, two of which grew invasively into the brain, suggesting that presence of a distinct rim of CSF around the meningioma indicates a histologically benign meningioma and its disruption suggests brain invasion.

Intra-operative assessment of tumor-brain interface

On classifying the tumor-brain interface at surgery in 52 (48 benign, 0 atypical and 4 anaplastic) meningiomas, Francesco et al,[57] found three kinds of interfaces namely smooth, transitional and invasive types. They correlated these intraoperative findings with the interface assessed on CT images which was again classified to three types, the first with no perifocal effects on brain had 13 cases, the second with perifocal halo like hypodensity had 21 and the third group characterized by finger like projections into the hemisphere had 18 patients. In all 18 cases of invasive types (100%) and 3 of the 21 transitional types (14.3%), they observed disruption of cerebral cortex intraoperatively. All the invasive type tumors correlated with finger like edema seen in pre operative CT scan. There were no cases of cortical disruption noted in 'smooth tumors'. Based on their findings they concluded that, prediction of the microsurgical effort needed for surgery of meningiomas can be made with the findings of type of hypodensity around the tumor on CT scan and stated that cerebral cortex penetration occurs in every case of invasive microsurgical-type meningioma and in a low percentage of (14.3%) transitional type meningiomas. However, it is clear from their observations that there is no correlation of the type of tumor-brain interface found at surgery

and the histological grade of the tumors, as there were only 4 WHO II/III tumors in the study and there were 18 cases of 'invasive' and 21 cases of 'transitional' type of tumor-brain interface that were identified. There was a statistically significant correlation of ambiguous tumor-brain interface with MIB-1LI in the study by Hashiba et al [3] Tumors with distinct peritumoral rim of CSF had MIB-1LI of 2.27% in comparison to those with indistinct tumor brain interface with a MIB-1LI of 3.8% ($p< 0.05$).

Summarizing, a few studies[55, 57] have indicated that disruption of the tumor-brain interface is associated with brain invasion, pointing to a higher histological grade.

Shape of the tumor

There are a number of studies that have correlated the shape of meningiomas to their biological behavior. [39, 54] The shapes of meningiomas have been described as round (smoothly curved surfaces pushing against the brain), lobulated (nodular surfaces pushing against the brain) and mushrooming meningiomas. [39] Mushrooming tumors were defined as having a prominent pannus extending over the cerebral surface from the globoid portion of the tumor [39]

Shape and tumor recurrence:

New et al, [39] first described the 'mushrooming' shape of meningiomas as identified on the CT images of the brain. Features that could be correlated with malignancy were assessed by reviewing the microscopic slides of 167 meningiomas. In cases with three or more recurrences, the number of mitoses counted under high power was higher than in those meningiomas showing clinically benign behavior. The radiologic and histologic features of seven meningiomas showing malignant clinical behavior and/or malignant histologic features were also evaluated and correlated. "Mushrooming," occurred in five of the seven malignant cases and was absent in the benign meningiomas that were reviewed

In a prospective study, [58] 101 meningiomas (1 anaplastic, 8 atypical and 92 benign) were followed up for at least 5 years after surgery. Recurrent meningiomas occurred in 17 patients. The study had 3 mushrooming, 22 lobulated and 74 round tumors. The shape of the tumor had a significant association with recurrence. All 3 tumors with mushrooming shapes (100%), 7 of the 22 lobulated tumors (31.8%) and 5 of the 74(6%) round tumors recurred. There was no significant difference in extent of excision in these three groups. These findings were corroborated by Idan et al, [59] who studied 201 patients with meningiomas where shape of the tumor, edema, calcification and vascularity were correlated studied to tumor recurrence and WHO grading. The tumor shape was categorized as round, lobulated, and mushrooming as in the previous study by Nakasu et al. [58] They found that tumor shape was statistically related to recurrence. Four of the six (66.6%) mushrooming tumors, 7 of the 28 (25.0%) lobulated tumors and only 5 of the 103 (4.8%) round tumors recurred. Time to recurrence was significantly longer for round tumors (105 months) and shorter for lobulated (87.5 months) and shortest for tumors with mushrooming. Furthermore, the four mushrooming tumors that recurred belonged to the WHO grade II/III group.

Quantification of irregularity of shape

Nawashiro et al [60] suggested quantification of irregularity of shape using an index called irregularity index (IR) defined as a ratio between the square of the perimeter and the area of the tumor. This index is low in circular tumors and higher in complex or irregular shaped tumors. They found a significant difference ($p = 0.001$) in the IR between benign meningiomas and atypical or anaplastic meningiomas. They also found a significant correlation between the IR and proliferative potential of the tumor as estimated based on MIB-1LI immunohistochemical findings.

Attempt at preoperative radiological score in a previous study

Hashiba et al [3] in a retrospective study with 90 cases of intracranial meningiomas compared preoperative MRI and CT findings with MIB-LI of the tumor. All the radiological images were studied by the first author and at least one of the 6 other authors. The radiological parameters studied by them were; location of the tumor, signal intensity, tumor size, contrast enhancement, perilesional edema, shape of tumor, tumor-brain interface and presence of calcification (as seen on CT scan).

The correlation between radiological parameters and high MIB-1LI was determined statistically and those with a positive correlation were later used for calculation of a preoperative radiological score. Only three factors had a positive correlation with the high MIB-1 index namely; the peritumoral brain edema, tumor-brain interface and irregular shape. Irregularly shaped tumor had a mean MIB-1LI of 4.6% and smooth shaped ones a mean MIB-1LI of 1.8% ($p= 0.0005$). Tumors with edema had a mean MIB-1LI of 3.8% and those without edema had a mean MIB-1LI of 2% ($p< 0.05$). Tumors with a distinct peritumoral rim of CSF had a MIB-1LI of 2.3% in comparison to those with an indistinct tumor brain interface with a MIB-1LI of 3.8% ($p< 0.05$). They thus devised a scoring system with these three radiological parameters as follows: smooth tumors = 0, irregular shaped tumors =1; Peritumoral edema present =1, absent = 0; Tumor-brain interface: indistinct = 1, distinct = 0. The total radiological score for each tumor was calculated. They had 32, 18, 19 and 21 patients with total radiological scores of 0, 1, 2 and 3 respectively. Their corresponding median MIB-1LI values were 1.3, 1.5, 1.6 and 2.7% indicating that there was steady increase in the mean MIB-1LI value with an increase in the total radiological score. Although the authors agreed to have differences in the scoring amongst themselves, the details of

individual scores by the observers and the inter observer variation was not available in the article. They did not classify the tumors into WHO Grades.

Recurrence rates

Simpson in 1957, [61] classified rate of recurrence based on extent of tumor resection. Simpson's Grade I removal is macroscopically complete, with excision of the dural attachment of the tumor and any abnormal bone. Grade II is the macroscopically complete removal of the tumor and its visible extensions, with coagulation of its dural attachment. Grade III is the macroscopically complete removal of the intradural tumor without resection or coagulation of its dural attachment or extradural extensions. Grade IV is a partial removal of the tumor, leaving the intradural portion of the tumor in place. Grade V is simple decompression of the tumor with or without a biopsy

In Simpson`s series of 265 meningiomas, he recorded a 21% recurrence rate (55 cases). The recurrence rates were 9% for grade I excision , 19% following grade II excision, 29% following grade III excision and 44% following grade IV excision. Based on Simpson`s Grading, subsequent studies have shown similar rtes of recurrence, depending on the extent of surgical resection. Mohammed et al [62] who followed up 25 cases of meningiomas for a period of 10 years found the recurrence rates to be 8% following grade I excision, 15% following grade II and grade III excisions, 29% recurrence following grade IV and 33% following grade V excision. Chan et al [10] found the recurrence rates to be 11% for grade I, 22% for grade II, 28% for grade III, 33% following grade IV excision and a 100% recurrence rate following grade V excision. These studies were depicting that the extent of tumor resection was the single most factor associated with tumor recurrence. They also correlated

that the degree of tumor resection in turn depended on the location of tumor. The convexity tumors had higher rates of complete resection in comparison to skull base tumors.

Aim

To predict the biological behavior of intracranial meningiomas based on the pre-operative Magnetic Resonance Imaging findings.

Objective

To correlate the MRI findings of intracranial meningiomas, namely, the peritumoral edema, tumor-brain interfaces and shape of the tumor with the MIB-1LI of the tumor.

Hypothesis

In meningiomas, MRI findings of peritumoral brain edema, ill-defined tumor-brain interface and irregular shape, predict an atypical / malignant tumor

Materials and Methods

Between January 2003 and June 2007, 373 patients underwent excision of intracranial meningiomas at our institution. Of them only 246 had a pre-operative MRI of the brain done either in our institute or elsewhere. All the cases had histopathological assessment, including immunohistochemistry done at our institute. 188 of the 246 cases were diagnosed to have WHO grade I (benign) meningiomas, 52 were diagnosed to have WHO grade II and 6 had WHO grade III meningiomas. They were grouped as Group A (benign) and Group B (atypical and malignant together)

A subset was made by matching every 2 patients from Group A with one patient of Group B, to reduce the sample size. The matching was based on the following criteria:

1. Age (+/- 5 years)

2. Gender

3. Location of the tumor (convexity/base of skull)

4. Size of the tumor (+/- 1 cm in any direction)

The subset had 132 patients after matching with patients of benign and malignant meningiomas in the ratio of 2:1. Five of these 132 cases were discarded from the study due to non-availability of T2W images or poor quality images. The final number of cases included in the study was thus 127. The list was randomized by arranging the names in alphabetical order and was presented in that order to the two neurosurgeons.

The pre-operative MRI brain of these patients were studied separately by two neurosurgeons (VR and AGC) focusing on three parameters namely, perilesional edema, tumor-brain interface and shape of the tumor. A score was assigned to each of the parameters as shown in **Table 4.** T2W axial images were used to assess the perilesional edema. The shape of the tumor and tumor brain interface was assessed on T2W images and T1w with gadolinium images.

The MIB-1LI of these tumors was assessed by a Neuropathologist (GC).

Immunohistochemical staining technique using monoclonal antibody to MIB-1 (DAKO Patts, Denmark) was performed as detailed in **Appendix 1**.

The two neurosurgeons were blinded to the MIB-1LI or any other aspects of the clinical and histopathological details for the tumor. There was no prior discussion between the two neurosurgeons regarding the three MRI parameters that were being assessed.

Results

The study included 127 (86 grade I and 41 grade II/III) intracranial meningiomas in 69 (54.3%) males and 58(45.7%) females, in the age group 20 – 68 years (mean 46.68; SD 10.46).

The MIB-1LI of the tumors ranged from 0.5 to 24% (mean 6.37; SD 5.43). The mean MIB-1LI was 11.8% for atypical and 3.8% for benign meningiomas, the difference in the two groups being statistically significant (p value = 0.0001) **(Figure 1).**

Table 5 classifies the tumors based on their MIB-1LI values using 7% as the cut off as indicated in our previous study.[22] Of the 127 cases, 50 had an MIB-1LI of ≥ 7% while 77 had an MIB-1LI of < 7%. Based on the WHO 2007 grading, of 127 total cases 41 were atypical and 86 were benign, since we had chosen them in a ratio of 1:2. The correlation between MIB-1LI and histological grade was assessed. Of the 41 atypical tumors, 36 had a MIB-1LI of ≥ 7 and 5 had a MIB-1LI < 7. From the total of 86 benign tumors, 72 had a MIB-1LI of < 7. It was calculated that MIB-1LI has a sensitivity of 87.8%, specificity of 83.7%, and positive predictive value of 72% and negative predictive value of 93.5% in correlation with histological grade of the tumor.

The three parameters namely perilesional edema, tumor-brain interface and shape of the tumor were recorded independently by two neurosurgeons and a total radiological score (minimum score of 0 and maximum score of 3) was assigned to each subject. **Appendix 4** shows the scores assigned to individual cases, for the three MRI parameters by both the observers.

The scores for each parameter:

Peritumoral Edema

Perilesional edema was present in 76 (59.8%) and absent in 51(40.1%) of total cases according to Observer 1, in comparison to 89(70.1%) where edema was present and 38 (29.9%) where it was absent according to Observer 2. Of the 76 cases with edema according to Observer 1, 24 were atypical and 52 were benign meningiomas as per the WHO 2007 grading. Out of the 89 cases in which Observer 2 had detected edema, 30 were atypical and 59 were benign. **(Table 6)**

Thus the sensitivity, specificity, positive predictive value and negative predictive value for edema in predicting atypical nature of meningiomas were 58.5%, 39.5%, 31.5% and 66.7% according to Observer 1; and 73.1%, 31.4%, 33.7% and 71.1% according to Observer 2. **(Table 8)**

On considering MIB-1LI of these cases **(Table 7)**, it was seen that of the 50 cases of MIB-1L1 more than 7, Observer 1 had detected edema in 32 cases and Observer 2 had detected edema in 37 cases. In the 77 cases with MIB-1LI less than 7, Observer 1 had stated absence of edema in 33 cases while Observer 1 had stated absence of edema in 25 cases.

Thus, according to Observer 1, edema had a sensitivity of 64%, specificity of 42.8%, and positive predictive value of 42.1% and negative predictive value of 64.7%. According to Observer 2, edema had a sensitivity of 74% and specificity of 32.4%, positive predictive value of 41.5% and negative predictive value of 65.7% in identifying a high MIB-1LI. **(Table 7, 8)**

Among the 50 meningiomas with MIB-1LI ≥ 7%, 31 meningiomas were found to have edema as per both observers; 11 to have no edema as per both observers; where as 8 were not matching; of these; according to Observer 1, 7 did not have any edema and 1 had edema; where as Observer 2 had stated 6 to have edema and 2 to not have edema.

In the MIB-1LI < 7 % group of 77 meningiomas; 42 were agreed upon to have edema and 23 to not have edema by the two observers; 12 were not matching; of which according to Observer 1, 10 had no edema and 2 had edema; where as Observer 2 found 2 to have no edema and 10 to have edema.

Tumor Brain Interface

Ill-defined tumor brain interface was seen in 12 (9.4%) and it was thought to be well defined in 115 (90.6%) of the total cases according to Observer 1, in comparison to 42(33.1%) ill-defined interface and 85 (66.9%) well defined interface for Observer 2.

Of the 12 tumors that Observer 1 had classified as ill-defined, 7 were atypical and 5 were benign meningiomas. Out of the 43 cases in which Observer 2 had recorded an ill-defined tumor-brain interface, 17 were atypical and 25 were benign. **(Table 9)**

Thus the sensitivity, specificity, positive predictive value and negative predictive value for tumor-brain interface in predicting atypical nature of meningiomas, according to Observer 1 was 12.2%, 91.9%, 41.7% and 68.7%; while according to Observer 2, it was 41.5%, 70.9%, 40.5% and 71.7%. **(Table 11)**

On considering the MIB-1LI of these cases, it was seen that of the 50 cases of MIB-1L1 ≥7, Observer 1 had detected ill-defined interface in 6 cases and Observer 2 had detected ill-defined interface in 19 cases. Out of 77 cases with MIB-1LI < 7, Observer 1 had detected well defined interface in 71 cases and Observer 2 had stated well defined interface in 54 cases. **(Table 10)**

Thus the sensitivity, specificity, positive predictive value and negative predictive value for tumor-brain interface, according to Observer 1 was 12%, 92.2%, 50.0% and 61.73%; and according to Observer 2, it was 38% ,70.1%, 45.2% and 63.3% in predicting a high MIB-1LI. **(Table 10)**

Presence of ill-defined brain tumor interface alone in the scan did not correspond to higher MIB-1LI in both the observations in statistically significant measures as per Chi square test. ($p = 0.428$ in Observer 1, $p = 0.341$ in Observer 2)

Looking into the levels of agreement on picking up ill defined brain tumor interface, out of the 50 meningiomas with MIB-1LI ≥ 7 %, 6 were agreed upon by both observers to have an ill defined brain tumor interface and 31 were agreed upon to have a well defined interface. However 13 observations were not matching; all of which were document to have well defined interface by Observer 1 and an ill defined interface by Observer 2 respectively.

In the group with an MIB-1LI < 7, 5 cases were agreed upon by both the observers to have ill-defined tumor-brain interface and 53 were agreed upon to have a well-defined tumor-brain interface. In the 19 that were not matching Observer 1 had stated that 18 of them had a well-defined interface and only one had ill defined interface; while Observer 2 had marked ill-defined interface for 18 and well-defined interface for one case only.

Shape of Tumor:

The tumor shape was classified as irregular in 28 (22.0%) and regular in 99 (78%) of the total cases according to Observer 1. According to Observer 2, 55(43.3%) were irregular shaped tumors and 75 (56.7%) regular shaped tumors.

Out of the 28 cases which the Observer 1 had recorded irregular shape, 14 were atypical and 14 were benign meningiomas. Out of the 55 cases which Observer 2 had recorded irregular shape, 24 were atypical and 31 were benign. **(Table 12)**

Thus the sensitivity, specificity, positive predictive value and negative predictive value for shape of tumor, according to Observer 1 was 34.1%, 83.7%, 50% and 72.7%; while it was 58.5%, 63.9%, 43.6% and 76.4% according to Observer 2 in predicting atypical nature of meningiomas**. (Table 14)**

On considering the MIB-1LI of these cases, it was seen that of the 50 cases of MIB-1L1 ≥7%, Observer 1 had detected an irregular shaped in 15 cases and Observer 2 had detected an irregular shape in 27 cases. Out of 77 cases with MIB-1LI of < 7% Observer 1 had detected regular shape in 64 cases and Observer 2 had stated regular shape in 49 cases. (Sensitivity of 30% and specificity of 83%, positive predictive value of 53.5% and negative predictive value of 64.65%). Observer 2 had a sensitivity of 54% and specificity of 63.6%, positive predictive value of 49.1% and negative predictive value of 68.1% in correlation with the MIB-1LI. **(Table 13)**

Presence of irregular shape of tumor alone in the scan did not correspond to higher MIB-1LI in the observations by Observer 1; in statistically significant measures as per Chi square test;

but was found to be significant as per Observer 2. ($p = 0.081$ in Observer 1, $p = 0.05$ in Observer 2)

Analyzing the inter observer agreement on findings of shape of tumor; out of the 50 meningiomas with MIB-1LI more than 7%; 14 were found to have an irregular shape of tumor by both observers, 22 had a regular shape by both observers; while 14 did not match. Of the 14 that did not match; 13 were marked to have a regular shape by Observer 1 and only one was irregular shaped; where as Observer 2 found only one to have a regular shape and 13 were irregular.

In the group of 77 meningiomas with MIB-1LI less than 7; 43 were agreed upon to have regular shape and 7 to have irregular shape by the two observers; 27 were not matching; of these 21 were stated to have regular shape by Observer 1 and 6 were stated to have a regular shape by Observer 2.

Combination of two parameters

Analysis of combination of two parameters was done among the study set of cases. Presence of both irregular tumor shape and ill defined brain tumor interface in each case corresponded to a higher MIB-1LI according to Observer 2. ($p = 0.05$ in Observer 2 and 0.3 in Observer 1) In correlation with histological grading, presence of both irregular shape and ill defined brain tumor interface was found to be statistically significant according to Observer 1. ($p = 0.05$ in Observer 1 and $p = 0.09$ in Observer 2) **(Figure 2, Table 15)**

The observations on each parameter was compared for each individual case as shown in the **Appendix IV**; findings on the WHO grade II / III meningiomas group cases are highlighted.

Table 16 shows the statistical significance of each of the three parameters which was calculated by performing Chi square tests, in cross tabulation with the MIB-1LI values. This showed that of the three parameters only shape of tumor had statistical significance (p=0.05) in one of the observers and the rest of the observations had no statistical significance.

Inter-observer Variation

The consistency of these observations was evaluated by calculating the inter-observer variability indicated by the 'Kappa' value for individual parameters and for the Total Radiological Score.

In observations on peritumoral edema, there was agreement on a total of 108 cases, thus showing that it has a good inter-observer agreement. (K=0.675) (**Table 17)**

There was agreement on 95 of 127 (K= 0.305) cases on tumor brain interface as shown in **Table 18**; the inter-observer agreement as shown by Kappa value being poor.

Similar cross tabulation for observations on shape of tumor showed an agreement on 21 irregular and 65 regular shapes of tumors out of 127 cases. The kappa was calculated to be 0.302, which is poor. (**Table 19)**

Table 20 shows the Total Radiological Scores for Observers 1 and 2. It is clear that the figures along the diagonal represent the number of patients in whom both observers assigned the same Total Radiological Score, which is 61/127 (48%). The figures to the left of the diagonal represent the number of cases in which Observer 1 quoted a score higher than Observer 2, that is 9/127 (7.1%), while those to the right of the diagonal depict the number of cases where Observer 2 quoted a score higher than Observer 1 that is 57/127 (44.9%).

Discussion

Introduction

Meningioma is the commonest benign intracranial tumor, accounting for 13–26% of all primary intracranial tumors.[1] They arise from the meninges, can progressively enlarge leading to compression of the surrounding neural tissue and cause neurological deficits, focal or generalized seizures.[6] Though generally benign in nature, these tumors could show aggressive behavior. A number of factors have been used to predict aggressive behavior in these tumors include age, gender, size and location of tumor, radiological characteristics histopathology and immunohistochemistry. The extent of tumor resection at surgery is classified based on Simpson`s [61] criteria and it has been shown in subsequent studies [10, 62] that tumor recurrence depends on Simpson`s Grade of tumor excision. A few studies [25, 26] have shown that the majority (60-65%) of patients with incidental meningiomas show no growth on follow up for 5 years. Therefore elderly patients, or those with high medical risk factors, with small asymptomatic tumors can be followed up on an annual basis. Prediction of the aggressiveness of these tumors therefore will help in appropriately counseling these patients towards most appropriate modality of treatment with radiosurgery emerging as a safe and effective option.

WHO GRADING

Meningiomas are classified into WHO grades I, II and III based on their histological characteristics. [1] One of the most commonly used classification and grading systems for meningiomas was set forth by the WHO in 2000 and was very recently updated in 2007. [1, 11] This system summarizes much of what is known about the features seen on routine histological examination that predict aggressive behavior in meningioma.

The WHO classification in 1993 [63] defined Grade II meningiomas as those "in which several of the following features are evident: frequent mitoses, increased cellularity, small cells with high nucleus/cytoplasm ratios and/or prominent nucleoli, uninterrupted patternless or sheet like growth, and foci of spontaneous or geographic necrosis." An anaplastic or malignant (Grade III) meningioma exhibited "histological features of frank malignancy far in excess of the abnormalities noted in atypical meningiomas." These definitions were vague and caused difficulty in classifying meningiomas. Independent researchers from Mayo clinic then, applied newer criteria; retrospectively reclassified their meningiomas previously classified by WHO 1993 criteria and found better correlation between histology and recurrence rates. The re-assessment resulted in change of grade in 13% of tumors and a 25% increase in Grade II tumors. [63] These criteria were applied in the WHO 2000 classification of meningiomas, which now included necrosis, as a feature of atypia. Subsequently brain invasion was included as a criteria for defining atypia and is the only significant change brought in the 2007 classification of meningiomas. [11]

Incidence of atypical /malignant meningiomas in literature

Owing to the repeated modification to the WHO classification, true incidence of atypical/ malignant meningiomas has not been determined. In 319 cases of meningiomas, 294 (92%) were found to be benign, 20(6.2%) were atypical and 5 (1.7%) were anaplastic. [62] Pearson et al [64] in their study of 440 meningiomas had 337 (77%) benign, 77 (17%) atypical and 41 (9%) anaplastic meningiomas.

In our study of 246 meningiomas, 188 (76.4%) cases were WHO grade I, 52 (21.1%) were WHO grade II and 6 (2.4%) WHO grade III meningiomas. The distribution was in accordance with the literature. The classification followed here is based on the criteria proposed by WHO 2000 classification of meningiomas.

MIB-1LI

As pointed out by various studies, there is a statistically significant correlation between high MIB-1LI values, histological grading and recurrence rates of meningiomas. [18, 19, 20] There have been studies showing higher incidence of atypical meningiomas and a higher range of MIB-1LI values in the pediatric age group. [23] A study from our institution showed that a cut-off value of 7% for MIB-1LI had highest validity in diagnosis of atypical meningiomas.[22] The cut-off for MIB-1LI used in various studies include 3 %, [23] 3.2%,[65] and 4.2%. [64]

Mitotic indices are known to correlate roughly with volume growth rate. [3] MIB-1LI shows a steady increase from benign through atypical to anaplastic varieties. [2, 3, 31, 62, 66] Certain studies showed values of MIB-1 LI to be ranging from 1·00–1·35% for grade I, to 1·9–9·3% for grade II or atypical, and 5·6–19·5% for grade III or anaplastic meningiomas [66]

MIB-1LI and WHO grading in our study

The mean MIB-1LI was 11.8% for atypical and 3.7% for benign meningiomas the difference in the two groups being statistically significant (p value = 0.0001). Out of the 127 cases, 50 had MIB-1LI of ≥7% and 77 had MIB-1LI of < 7%. Of the 41 atypical tumors in the study, 36 had a MIB-1LI of ≥ 7% while of the 86 benign tumors, 72 had a MIB-1LI of <7%. Thus MIB-LI had a sensitivity of 87.8% and specificity of 83.7%, making it a useful additional tool to the WHO grading system.

Radiological features:

Peritumoral brain edema

Numerous studies in the past have correlated PTBE with various clinico-pathological parameters in meningiomas. [28, 38, 31, 39-50] The various factors that are thought to play a role in the PTBE associated with meningiomas include size of the tumor, histological subtype, vascularity, level of growth factors like VEGF, venous stasis and brain invasion. [42, 43, 44] Ide et al [42] who studied 57 cases of intracranial meningiomas and found that edema was significantly correlated with MIB-1LI and tumor size. Lee et al [47] correlated edema with histological grade (grade I vs. grade II/III) of WHO histological subtypes. On the other hand, Chen et al [31] found no correlation between the degrees of surrounding edema or contrast enhancement with histopathological findings. Simis et al [67] showed that peritumoral edema had a positive correlation with high recurrence rates (p=0.042) but did not comment on the MIB-1LI or histological grading.

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Despite many studies on peritumoral brain edema, in meningiomas, the exact etiology remains elusive. Studies that have considered size of the tumor as a possible etiology have not shown consistent correlation, [47, 48, 49] as there were small meningiomas with large amount of edema and very large meningiomas with negligible edema. A few studies [44, 49, 50] have considered proximity of tumor to venous sinuses as another factor causing edema, but others have not supported this theory. [44] The correlation of peritumoral brain edema with WHO grade of the tumor is also poor, although studies [42, 47] have shown that higher grades of edema is seen with higher WHO grade of the tumor. This finding is not restricted to atypical meningiomas as high grades of edema have been associated with certain benign variants too. [44, 45, 46]

Our study did not show any correlation between the presence of peri-lesional edema and a high MIB-1LI (>7%) from the findings of both observers. The negative predictive value was too low (64.5 and 65.7 for Observer 1 and Observer 2 respectively) thus suggesting that the absence of peritumoral edema cannot be an indicator of benign nature of meningiomas. It was noted that the first observer had stricter criteria for definition of presence of edema and the Observer 2 was more general in his definition of presence of edema. This enabled Observer 2 to pick more cases of edema in the group with MIB-1LI more than 7%, giving him a higher sensitivity (74% in comparison of 64% for Observer 1) but he had to compromise on specificity (32.4% in comparison to 42.8% for Observer 1.) It is notable that this parameter had maximum inter observer agreement with a Kappa of 0.67. **Figure 3** shows a T2W image showing a large meningioma with no edema around it as agreed upon by the two observers of our study and **Figure 4** shows MRI of patient with parasagittal meningioma which had disagreement between the observers for presence of edema. Observer 1 recorded it to have edema where as Observer 2 recorded it as a case with no peritumoral brain edema.

Tumor-brain interface

Although several studies report on tumor-brain interface of meningiomas, [41, 52, 54, 56, 58] only a few of them have attempted a correlation with the with biological behavior of these tumors. [52, 58] These latter studies have found that an indistinct tumor-brain interface on imaging is associated with recurrent meningiomas. Hashiba et al [3] found that the tumors with a distinct peritumoral rim of CSF had a lower mean MIB-1LI of 2.3% in comparison to those with an indistinct tumor-brain interface which had a mean MIB-1LI of 3.7% and this to be statistically significant. Our study showed that presence of ill-defined tumor-brain interface alone in the scan did not correspond to higher MIB-1LI. This parameter in our study had a high specificity of 92% but a very low sensitivity of 12% for Observer 1 and moderate specificity of 70.1 and low sensitivity of 38% for Observer 2 in predicting tumors with MIB-1LI≥7%. However, the inter-observer variability for this parameter was high as suggested by the Kappa value of 0.305. **Figure 5** shows MRI of patient with well defined tumor-brain interface as agreed upon by both the observers and **Figure 6** shows MRI of a pterional meningioma with disagreement between the observers for tumor-brain interface.

Shape of the tumor

Various studies in literature have classified tumor-brain interface as round, lobulated and mushrooming type [2, 39, 54] The shape of tumor was classified as round (smoothly curved surfaces pushing against the brain), lobulated (nodular surfaces pushing against the brain) and mushrooming meningiomas. Mushrooming tumors were defined as having a prominent pannus extending over the cerebral surface from the globoid portion of the tumor [39]

Shape and tumor recurrence:

Nasaku et al [54] followed up 100 patients who underwent gross total removal of meningiomas for at least 5 years or until tumor recurrence. Preoperative radiological findings and clinical characteristics were assessed. On univariate analysis, tumor size and shape, relation to the major sinuses, calcification, bone changes and characteristics of the tumor-brain interface were significant predictive factors for recurrence. Multivariate analysis revealed that only the shape of the tumor was significant; both mushrooming and lobulated meningiomas were more likely to recur than the round ones.

In another study Idan et al [59] studied 201 patients of meningiomas where shape of the tumor, edema, calcification and vascularity were studied with respect to tumor recurrence, that occurred in 16 patients An irregular tumor shape was the only factor that was associated with recurrence. Moreover, mushrooming appeared to be the radiological finding that strongly correlated with the higher WHO grade, and this finding seemed to be corroborated by other authors. [2, 39]

Irregularity Index

Nawashiro et al [60] suggested quantification of irregularity of shape using an index called irregularity index (IR) defined as a ratio between the square of the perimeter and the area of the tumor. This index would be least in a tumor with circular shape and higher in irregular tumors. They found that IR was significantly higher in the atypical and anaplastic meningiomas compared to the benign variety. They also found a significant correlation between the IR and MIB-1LI.

We found that a tumor with an irregular shape had a statistically significant correlation with higher MIB-1LI for Observer 2 ($p=0.05$) but not for Observer 1. The shape of the tumor had a high specificity of 83% and a low sensitivity of 30% in Observer 1 and a sensitivity of 53% and specificity of 63.6% in Observer 2, in correlation with MIB-1LI values. This highlights the fact that Observer 1 had stricter criteria for defining irregular shape. On the other hand, Observer 2 was more liberal in defining irregular shape, resulting in a slightly better sensitivity, but lost out on specificity in comparison with Observer 1. Out of the 50 meningiomas with MIB-1LI $\geq$ 7%, 14 were found to have an irregular shape of tumor by both observers, 22 had a regular shape by both observers; while 14 did not match. The inter-observer variability was high for this parameter, suggested by a kappa of 0.302. **Figure 7** shows a meningioma with irregular shape as agreed upon by both the observers, where as **figure 8** shows a meningioma with disagreement between the observers for the tumor shape.

Combination of Shape and tumor-brain interface

Analyzing the outcome by combining two of these parameters, namely shape of the tumor and tumor-brain interface; we found that the results were statistically significant in correlation with MIB-1LI values for Observer 2 ($p=0.05$) and with WHO grading for Observer 1 ($p=0.05$). Thus, combination of these two parameters correlated with the biological behavior better than when they were considered separately.

Previous study on pre-opeative radiological scoring for meningiomas

Hashiba e t al [3] in their study on 90 cases, found statistically significant positive correlation of MIB-1LI with shape of the tumor, with the mean MIB-1LI of irregularly shaped tumors being higher (4.6%) than regular shaped ones (1.8%). Similarly it was seen that tumors with edema and indistinct tumor brain interface had higher MIB-1LI. They devised a scoring system with these three radiological parameters and the total radiological score (TRS) was calculated. They had 32, 18, 19 and 21 patients with total radiological scores of 0, 1, 2 and 3 respectively. Their corresponding median MIB-1LI values were 1.3, 1.5, 1.6 and 2.7%. Although there was an increase in the mean MIB-1LI values with increasing total radiological score, it can be noted that the difference between the mean MIB-1LI for the lowest TRS and highest TRS was minimal. These authors did not use the WHO grading system. The authors concluded that TRS could not be applied clinically, in view of the high inter-observer variation. Our study also showed a high inter-observer variation with TRS.

Inter-observer variation

The consistency of these outcomes in routine clinical practice is questionable as indicated by the high inter-observer variability for all parameters except perilesional edema. This is shown in **Table 20**, (page 43) which tabulates the total radiological scores for Observers1 and 2. It is clear that the figures along the diagonal represent the number of patients in whom both observers assigned the same total radiological score that is 61/127 (48.0%). The figures to the left of the diagonal represent the number of cases in which Observer 1 quoted a score higher than Observer 2, that is 9/127 (7.1%),while those to the right of the diagonal depict the number of cases where Observer 2 quoted a score higher than Observer 1 that is 57/127 (44.9%). This reflects the fact that the observers differed greatly in how strictly they applied each of the three parameters, and that Observer 1 used very strict criteria while Observer 2 had more general criteria. As discussed earlier, an ideal screening tool should fulfill the essential criteria of repeatability and validity, which in turn depends on good sensitivity and specificity. The observers in our study were not given standardized criteria for recognition of the various radiological parameters on the MRI and this could have contributed towards the high inter-observer variability.

Summary

Perilesional edema – There is good inter-observer agreement but no statistical significance in predicting high MIB-1LI or histological grade of meningiomas.

Tumor Brain interface – This parameter has high specificity in detecting atypical meningioma for Observer 1, but it also has high inter observer variability. Moreover it has a low sensitivity which makes it a bad screening tool for detecting aggressive nature of meningiomas.

Shape of tumor – This has high specificity for Observer 1 and statistical significance in predicting high MIB-1LI in Observer 2. Irregular shape of tumor has good positive predictive value for atypical meningiomas. But even this parameter was found to have a high inter observer variability and low sensitivity; thus making it an inappropriate screening tool for picking up atypical nature of meningiomas pre-operatively.

Combination of tumor brain interface and shape When used concurrently, tumor brain interface and shape of tumor was found to have a statistically significant correlation with

MIB-1LI and histological grading.

Total Radiological Score also exhibited a high inter observer variability rendering it unfit to be used on a regular basis for prediction of biological behavior of meningiomas pre operatively. This was probably because of peritumoral edema.

It is possible that standardization of the radiological criteria may ensure uniform recognition and may improve the inter observer variation, but may not contribute to improving the sensitivity and specificity. This is because Observer 1 and Observer 2 represent extremes in the spectrum of preoperative diagnosis, with Observer 1 being very strict obtaining a high specificity but a low sensitivity and Observer 2 being more liberal and yet not being able to raise the sensitivity to acceptable levels. A good screening tool should fulfill the essential criteria of acceptability, repeatability and validity. A screening tool is considered to be valid based on its sensitivity and specificity. These two parameters along with accuracy form the inherent properties of screening test. Sensitivity is the ability of the test to identify correctly all that is "true positives" and specificity is the ability of the test to identify correctly all that is " true negatives" An ideal screening tool should be 100% sensitive and 100% specific, but in practice a test with a high sensitivity and moderate specificity is acceptable. In this study we find that the sensitivity of the MR findings was highest for edema (70%), while for other parameters the sensitivity was very poor making it a poor screening test.

Drawbacks of the study:

The study was retrospective. MR images from outside centers were also included in the study, causing variability in the quality of the images. There was no standardization of criteria for identification of various parameters on the images. Statistically better inter-observer agreement may have been expected had there been standardization in scoring for each parameter. No attempt was made to quantify the radiological parameters.

Recommendations:

A prospective study with uniformity in the MR imaging in terms of the sequences that are studied is needed. The probability of identifying peritumoral edema may be better when both

T2W and FLAIR images are used for studying the perilesional edema in all patients. Unlike in a retrospective study a prospective study can ensure that all the patients have the required sequences of MRI. Similarly, the efficacy of identifying tumor-brain interface and shape of tumor will be better if all patients had contrast images.

Quantification of each parameter:

1. Edema: Calculation of edema index may help in grading the edema. The grade of edema probably will have better correlation with MIB-1LI than just its presence or absence. Quantification also has the likelihood of decreasing the inter-observer variability.

2. Tumor- brain interface should have been assessed from post contrast MRI images and this probably would have decreased the inter-observer variability. There should be a method of grading tumor- brain interface, probably in terms of ratio of the perimeter of the surface of the tumor that has ambiguous interface with brain, in relation to total perimeter of the tumor. There have been no studies in literature that has looked into this aspect. Does the extent of indistinct tumor-brain interface in the tumor correlate better with the higher MIB-1LI than just presence or absence of indistinct tumor-brain interface?

3. Shape of tumor: The Irregularity index, [60] could be applied to quantify the irregularity of tumor. This quantification may help in reducing the inter-observer variability on this parameter, and improve the positive predictive vaue.

Conclusion

Magnetic resonance image finding of irregular tumor shape was found to have a statistically significant correlation with high MIB-1LI of meningiomas. An irregular tumor in combination with poor tumor-brain interface positively correlated with atypical /malignant meningiomas. However, the high inter-observer variability and low sensitivity associated with these observations warrants standardization and quantification of radiological parameters before they may be applied in clinical practice.

Table 1 Distribution of Intracranial Meningiomas in Cushing's series. [4]

Location of tumor	**Incidence**
Convexity	34%
Parasagittal	22%
Sphenoid ridge	17%
Lateral ventricular	5%
Tentorium	4%
Cerebellar convexity	5%
Tuberculum sellae	3%
Intraorbital	2%
Cerebellopontine angle	2%
Olfactory groove	3%
Foramen magnum	1%
Clivus	1%

Table 2: Summary of the 2007 WHO Grading Scheme for Meningiomas [11]

WHO GRADE	HISTOLOGICAL SUBTYPE	HISTOLOGICAL FEATURES
I	Meningothelial Fibroblastic Transitional Angiomatous Microcystic Secretory Lymphoplasmacytic Metaplastic Psammomatous	The tumors in this grade do not fulfil the criteria for Grade II or III
II	Chordoid Clear cell	There are 4 or more mitotic cells per 10 high power fields and/or 3 or more of the following: increased cellularity, small cells, necrosis, prominent nucleoli, sheeting, and/or brain invasion in an otherwise Grade I tumor
III	Papillary Rhabdoid	There are 20 or more mitoses per 10 high power field and/or obviously malignant cytological characteristics such that tumor cell resembles carcinoma, sarcoma, or melanoma

Table 3 Histologic and immunohistochemical features of prognostic significance in meningiomas

Absence of immunoreactivity for progesterone receptors.
Loss of lobular pattern (sheeting)
Hypercellularity
Cytologic atypia with macronucleoli
Increased mitotic rate (>/= 4/10 high power field)
Necrosis (in the absence of prior embolization)
Elevated MIB-1index
Small cell change
Invasion of the brain
Cellular anaplasia
Histologic subtype (Rhabdoid, papillary, chordoid, clear cell)
Absence of immunoreactivity for progesterone receptors.

Table 4 Criteria for radiological scoring

CRITERIA		
Perilesional edema	Absent = 0	Present = 1
Tumor-brain interface	Well defined = 0	Ill-defined = 1
Shape of tumor	Regular = 0	Irregular = 1

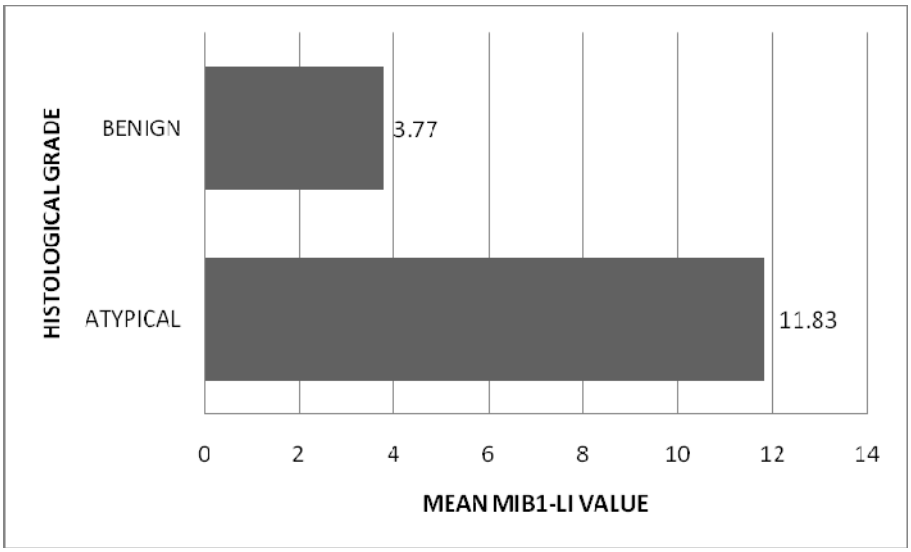


Fig 1 *Correlation between MIB-1 labeling index and histological grading of the meningiomas*

Table 5: Correlation between MIB1-LI and histological grading showing its significance.

MIB-1 LI VALUE	**HISTOLOGICAL GRADING**			
	Atypical	**Benign**	**Total**	
≥7 %	36	14	**50**	**PPV**= 72
< 7%	5	72	**77**	**NPV**= 93.5
Total	**41**	**86**	**127**	
	Sensitivity= 87.8	**Specificity** = 83.7		

Table 6 Identification of perilesional edema in the study set by the two observers, in relation to WHO grading

EDEMA	Observer 1		Observer 2	
	WHO I	WHO II/III	WHO I	WHO II/III
Present	52	24	59	30
Absent	34	17	27	11

Table 7 Peritumoral edema crosstabulated against MIB-1LI for the two observers

Observer 1	**MIB-1LI**		
EDEMA	**≥7(n=50)**	**< 7(n=77)**	
PRESENT	32	44	**Positive predictive value= 42.1%**
ABSENT	18	33	**Negative predictive value= 64.7%**
	Sensitivity=64%	**Specificity=42.8%**	
Observer 2	**MIB-1LI**		
EDEMA	**≥7(n=50)**	**< 7(n=77)**	
PRESENT	37	52	**Positive predictive value= 41.5%**
ABSENT	13	25	**Negative predictive value= 65.7%**
	Sensitivity=74%	**Specificity=32.4%**	

Table 8 Various statistical parameters on significance of edema with respect to MIB1-LI and WHO grade as per the two observers

	Observer 1 (%)		**Observer 2 (%)**	
	MIB-1LI	WHO GRADE	MIB-1LI	WHO GRADE
Sensitivity	64	58.5	74	73.1
Specificity	42.8	39.5	32.5	31.4
Positive Predictive Value	42.1	31.5	41.5	33.7
Negative Predictive value	64.7	66.7	65.7	71.1

Table 9 Tumor-Brain interface as observed by the two observers in relation with WHO grading

TUMOR-BRAIN INTERFACE	Observer 1		Observer 2	
	WHO I	WHO II/III	WHO I	WHO II/III
Ill-defined	7	5	25	17
Well defined	79	36	61	24

Table 10 Tumor-Brain interface cross tabulated against MIB-1LI for the two observers

Observer 1	MIB-1 LI		
Tumor-brain interface	≥7(n=50)	< 7(n=77)	
Ill-defined margins	6	6	Positive predictive value = 50%
Well defined margins	44	71	Negative predictive value = 61.7%
	Sensitivity=12%	Specificity=92.2%	

Observer 2	MIB-1 LI		
Tumor-brain interface	≥7(n=50)	< 7(n=77)	
Ill-defined margins	19	23	Positive predictive value =45.2%
Well defined margins	31	54	Negative predictive value =63.2%
	Sensitivity=38%	Specificity=70.1%	

Table 11 Various statistical parameters on significance of tumor-brain interface with respect to MIB1-LI and WHO GRADE as per the two observers

	Observer 1 (%)		Observer 2 (%)	
	MIB-1LI	WHO GRADE	MIB-1LI	WHO GRADE
Sensitivity	12	12.2	38	41.5
Specificity	92.2	91.9	70.1	70.9
Positive Predictive Value	50	41.7	45.2	40.5
Negative Predictive value	61.7	68.7	63.2	71.7

Table 12 Shape of tumor in correlation with their WHO grading

TUMOR SHAPE	Observer 1		Observer 2	
	WHO I	WHO II/III	WHO I	WHO II/III
Irregular	14	14	31	24
Regular	72	27	55	17

Table 13 Tumor shape cross tabulated against MIB-1LI for the two observers.

Observer 1	MIB-1LI		
Tumor Shape	≥7(n=50)	< 7(n=77)	
Irregular	15	13	Positive predictive value=53.5 %
regular	35	64	Negative predictive value= 64.6%
	Sensitivity=30%	Specificity=83%	
Observer 2	MIB-1LI		
Tumor Shape	≥7(n=50)	< 7(n=77)	
Irregular	27	28	Positive predictive value=49.1%
Regular	23	49	Negative predictive value=68.1%
	Sensitivity=54%	Specificity=63.6%	

Table 14 Various statistical parameters on significance of **shape of tumor** with respect to MIB1-LI and WHO GRADE as per the two observers

	Observer 1 (%)		Observer 2 (%)	
	MIB-1LI	WHO GRADE	MIB-1LI	WHO GRADE
Sensitivity	30	34.1	54	58.5
Specificity	83	83.7	63.6	63.9
Positive Predictive Value	53.5	50	49.1	43.6
Negative Predictive value	64.6	72.7	68.1	76.4

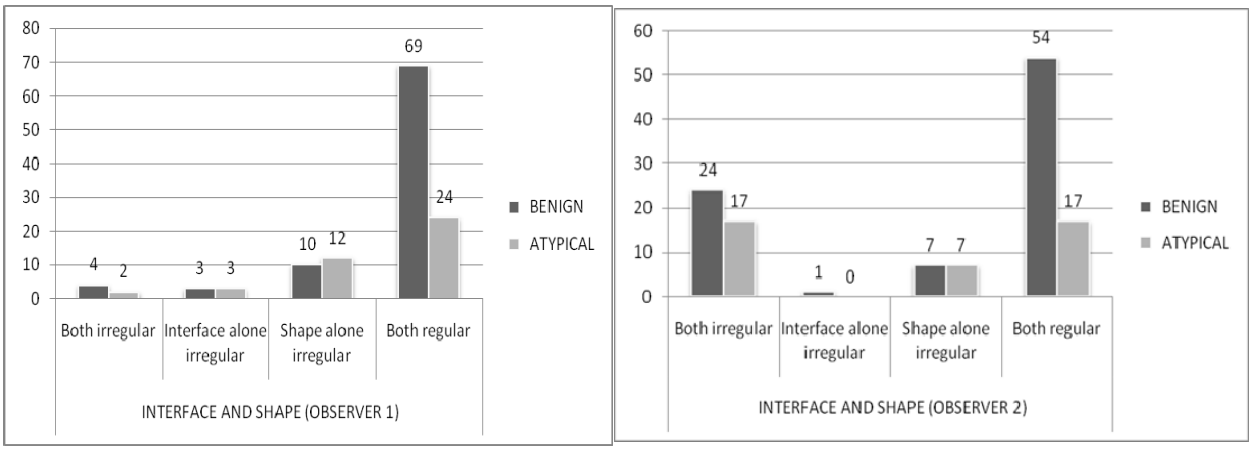


Figure 2: *Observations on combination of two parameters; shape of tumor and tumor-brain interface*

Table 15 Combination of tumor-brain interface and tumor shape in comparison with the MIB-1 LI as per the two observers

MIB-1 LI value	Observer 1 Both shape and interface irregular	Observer 2 Both shape and interface irregular	Observer 1 Interface alone irregular	Observer 2 Interface alone irregular	Observer 1 Shape alone irregular	Observer 2 Shape alone irregular	Observer 1 Both regular	Observer 2 Both regular
≥7(n=50)	**3**	**18**	**3**	**1**	**12**	**9**	**32**	**22**
< 7(n=77)	**3**	**23**	**3**	**0**	**10**	**5**	**61**	**49**

Table 16 Statistical significance of edema, tumor-brain interface and shape of tumor in correlation with MIB1-LI (p values obtained by performing Chi square tests)

	p value (Observer 1)	**p value (Observer 2)**
Peritumoral edema	0.441	0.437
Tumor-brain interface	0.428	0.341
Shape of tumor	0.081	0.05

Table 17 Crosstabulation for peritumoral edema as per the two observers

	Observer 2		
Observer 1	**"Present"**	**"Absent"**	**Total**
"Present"	73	3	76
"Absent"	16	35	51
Total	89	38	127

K =0.675

Table 18 Crosstabulation for tumor-brain interface as per the two observers

	Observer 2		
Observer 1	**Ill defined**	**Well defined**	**Total**
Ill defined	11	1	12
Well defined	31	84	115
Total	42	85	127

K= 0.305

Table 19 Cross tabulation for tumor shape as per the two observers

	Observer 2		
Observer 1	**Irregular**	**Regular**	**Total**
Irregular	21	7	28
Regular	34	65	99
Total	55	72	127

K=0.302

Table 20 Cross tabulation between the total radiological scores as interpreted by the two observers

K = 0.285		**Observer 2 total score**				
		0	**1**	**2**	**3**	
Observer 1 total score	**0**	**23**	11	7	0	
	1	4	**30**	9	16	
	2	1	4	**5**	14	
	3	0	0	0	**3**	
Total						127

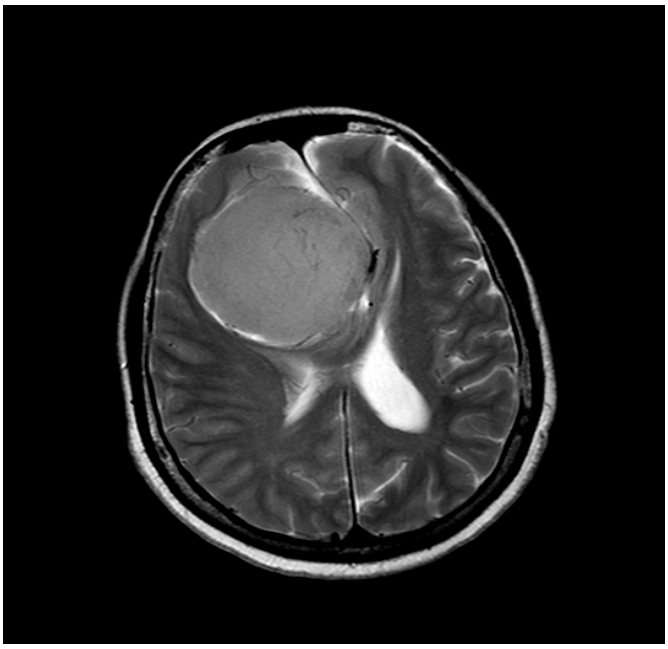


Figure 3: T2W MRI showing large meningioma with no peritumoral edema as agreed upon by both the observers.

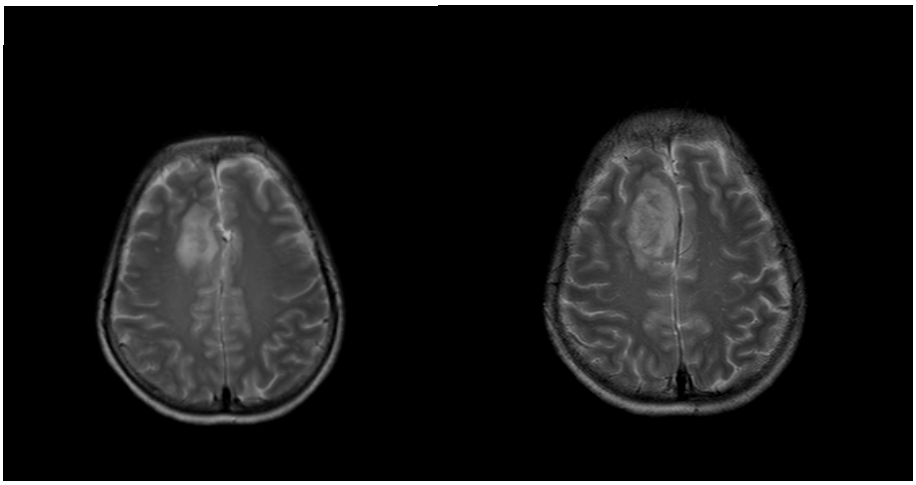


Figure 4 Parasagittal meningioma with disagreement on presence of edema between the observers.

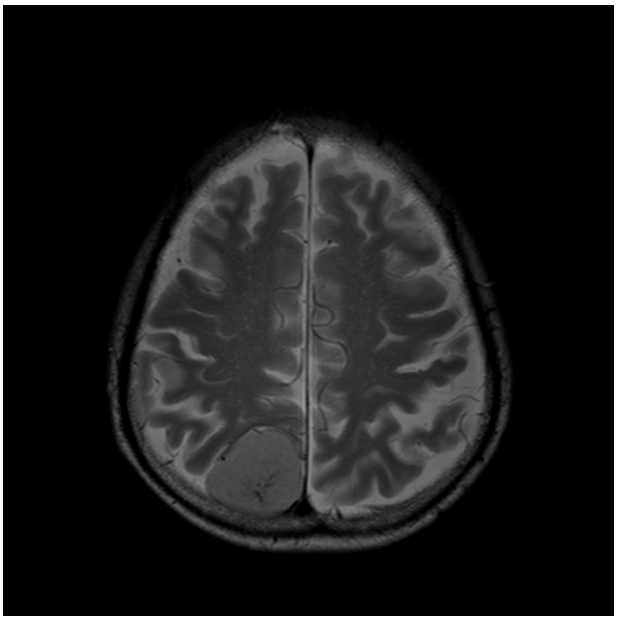


Figure 5 Meningioma with well defined tumor-brain interface as agreed upon by both observers.

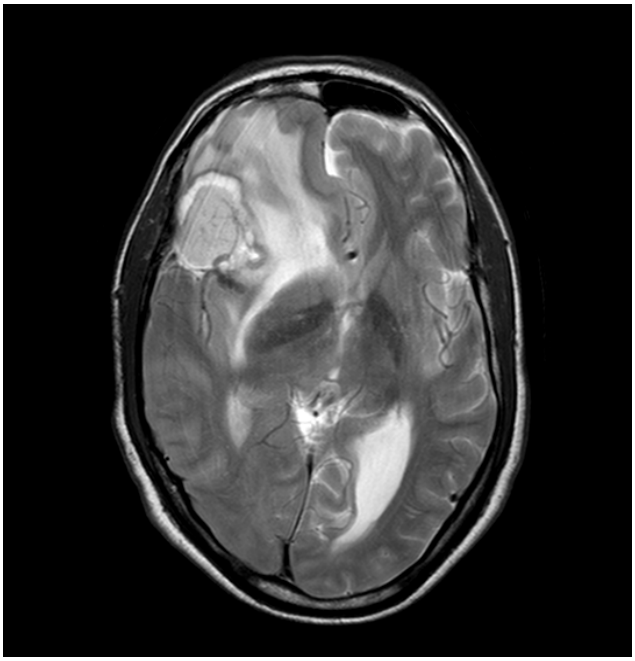


Figure 6 Meningioma with disagreement between observers for tumor-brain interface. Histopathology of this tumor was Angiomatous meningioma, WHO grade I, with MIB-1 proliferating index of 4%,

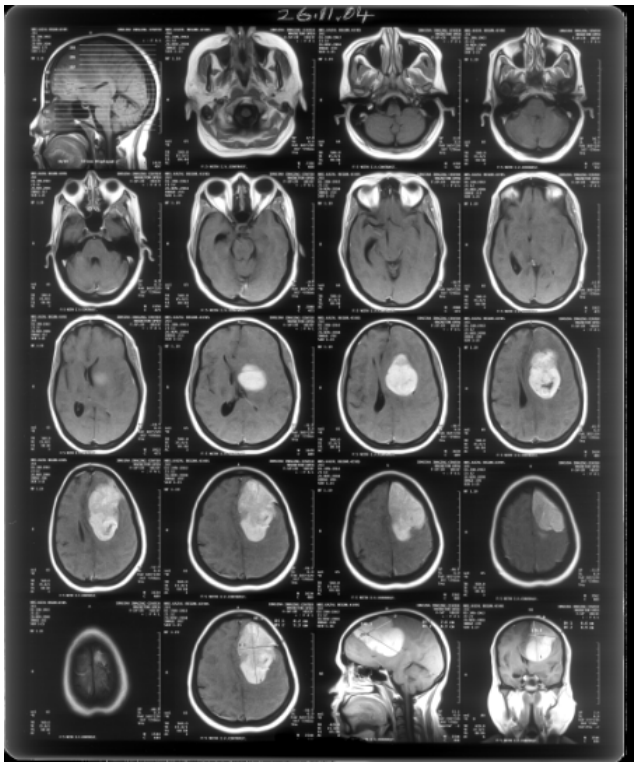


Figure 7 showing a meningioma with irregular shape as agreed upon by both observers. Histology was consistent with chordoid meningioma, WHO grade II, MIB-1LI 10%

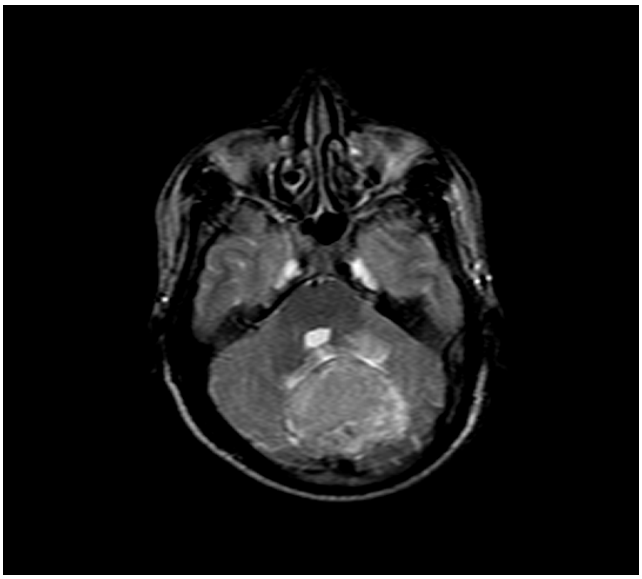
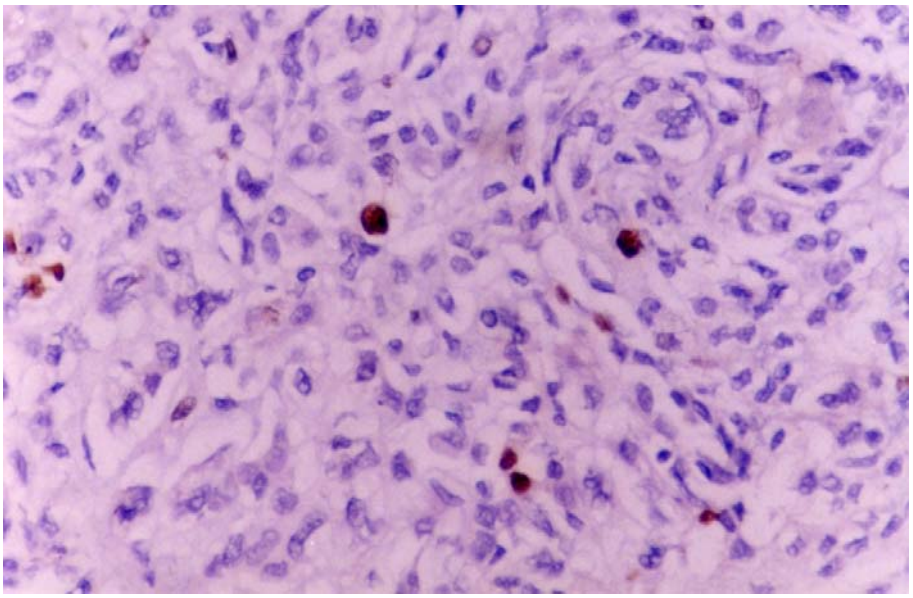
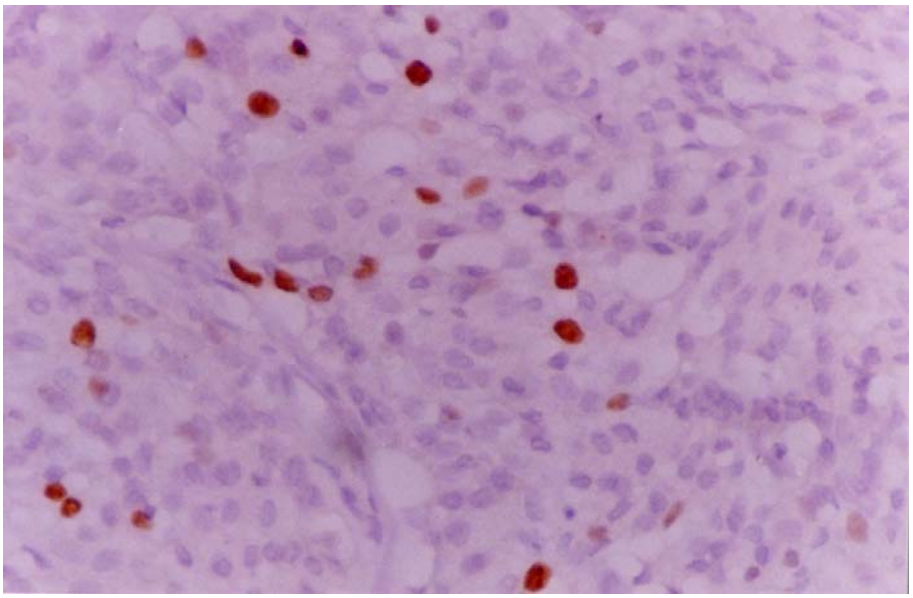


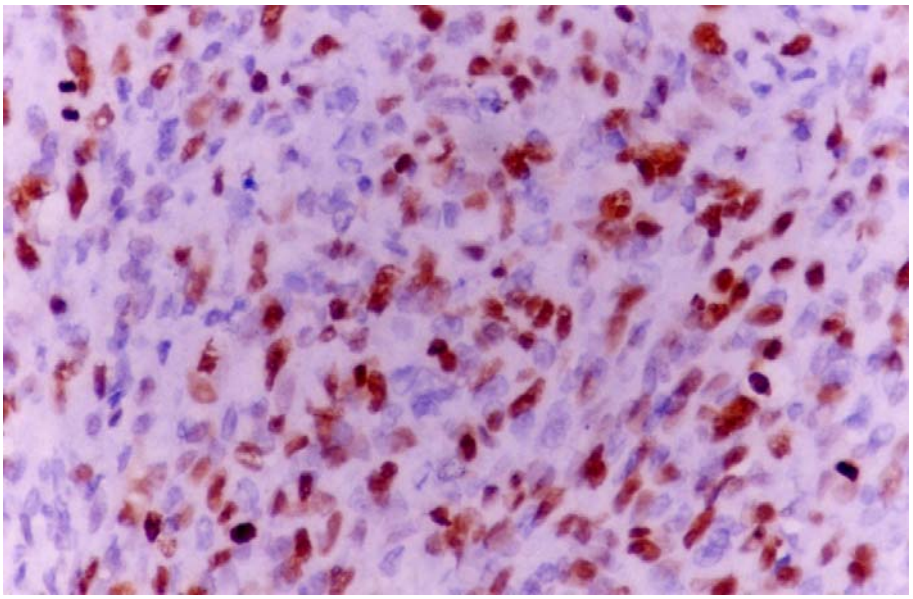
Figure 8: Showing a meningioma with disagreement between the observers for irregularity of shape. Observer 1 called it irregular and observer 2 called it regular. Histopathology was consistent with WHO grade 1 with MIB 1 proliferation index 9%



Immunohistochemistry staining of meningioma showing a MIB-1LI of 1%



Immunohistochemistry staining of meningioma showing a MIB-1LI 7%



Immunohistochemistry staining of meningioma with MIB-1LI of 40%

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Appendix -1

Methodology of MIB-1 index assessment:

Representative 5µ sections of each case were mounted on poly-L-Lysine coated slides and incubated overnight at 370˚C. Sections of tonsil were used as positive control. Negative controls were achieved by omitting the primary antibody. Sections were deparaffinized followed by rehydration in decreasing ethanol concentrations and placed in distilled water. Antigen retrieval was done by pressure cooking.13 10mM sodium citrate (pH 6.0) was boiled in a pressure cooker. The slides were placed in the boiling buffer and the lid of the pressure cooker closed. The cooker was allowed to come to full pressure. After 2 minutes of boiling at full pressure, the cooker was cooled by quenching in cold running tap water. The slides were then removed quickly and placed in distilled water for 2 changes and allowed to cool to room temperature, and then transferred to 0.05 M Tris (Aldrich) buffered saline (pH 7.4), care being taken to ensure that the slides did not dry. The slides were individually drained of buffer, by gentle tapping, followed by careful wiping of excess liquid around the section. The sections were then covered with normal human pooled serum (1:5 dilution, Institutional Blood Bank) and incubated for 15 minutes. All excess liquid was drained off the slide by gentle tapping and the sections covered with the diluted MIB-1 monoclonal antibody (DAKO Patts, Denmark), at a dilution of 1:75 and incubated for 30 minutes at room temperature (240C). The slides were then rinsed in Tris-buffered saline 3 times for 5 minutes each. The sections were then drained and covered by diluted secondary antibody, biotinylated rabbit anti mouse (1:200 dilution, DAKO Patts, Denmark) and incubated for 30 minutes at room temperature. The slides were then rinsed in Tris-buffered saline 3 times for 5 minutes each. Endogenous peroxidase was blocked with 0.5% hydrogen peroxidase (Qualigens) in methanol by incubating the slides covered with solution for 30 minutes. The sections were rinsed in Tris-buffered saline 3 times, for 5 minutes each. The sections were then drained and

covered with peroxidase conjugated avidin (1:200 dilution, DAKO Patts, Denmark) and incubated for 30 minutes. The slides were rinsed with 3 changes of Tris-buffered saline for 5 minutes each. The slides were then developed using freshly prepared diaminobenzidine tetrahydrochloride solution (DAKO Patts, Denmark) containing hydrogen peroxide, for 10 minutes. At this point positive controls were checked to ascertain the end of incubation. The sections were counterstained with Harris Hematoxylin for 10 seconds. The sections were then dehydrated, cleared, and mounted with DPX as mounting medium. Cells with brown nuclei were considered immunopositive for MIB-1.

APPENDIX 2

PROFORMA

Prediction of MIB-1 index based on radiological criteria

CASE NUMBER:

HOSPITAL NUMBER:

RADIOLOGICAL SCORE

CRITERIA			**SCORE**
Peritumoral edema in MRI	Absent	Present	
Brain tumor interface on MRI	Well defined	Ill-defined	
Shape of tumor on MRI	Regular	Irregular	

TOTAL SCORE:

PATHOLOGY

BIOPSY NUMBER

HISTOLOGICAL GRADING

WHO I	**WHO II**	**WHO III**
Meningothelial meningioma		
Fibrous	Atypical	Rhabdoid
Transitional		
Psammomatous	Clear cell	Papillary
Angiomatous		
Microcystic		
Secretory	Chordoid	Anaplastic
Lymphoplasmocyte – rich		
Metaplastic		

MIB-1 INDEX:

Appendix 3

Radiological Scoring of the study set of 127 cases by the two observers, their MIB1 LI value and histological grading

PATIENT NO:	EDEMA		TUMOR- BRAIN INTERFACE		SHAPE		TOTAL SCORE		GRADE	MIB-1LI
	Observer1	Observer2	Observer1	Observer2	Observer1	Observer2	Observer1	Observer2		
1	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**A**	**9**
2	**1**	**1**	**0**	**0**	**1**	**1**	**2**	**2**	**A**	**15.1**
3	1	1	0	1	0	1	1	3	T	5.4
4	1	1	0	0	0	0	1	1	T	1
5	0	0	0	0	0	0	0	0	T	1
6	1	1	0	0	0	0	1	1	T	11
7	1	1	0	1	0	1	1	3	T	3
8	**0**	**1**	**0**	**0**	**0**	**0**	**0**	**1**	**A**	**10**
9	**1**	**1**	**1**	**1**	**0**	**1**	**2**	**3**	**A**	**8**
10	1	1	1	0	0	0	2	1	T	2.8
11	1	1	0	0	0	1	1	2	T	3
12	1	1	0	0	0	0	1	1	T	6
13	0	1	0	0	0	0	0	1	T	2

14	1	1	0	0	0	0	1	1	T	2
15	1	1	1	1	1	1	3	3	T	3
16	0	0	0	1	0	1	0	2	T	5
17	1	1	0	1	0	1	1	3	T	4.8
18	**1**	**1**	**0**	**1**	**0**	**1**	**1**	**3**	**A**	**8**
19	0	1	0	0	0	0	0	1	T	2
20	**1**	**1**	**0**	**1**	**1**	**1**	**2**	**3**	**A**	**7**
21	**1**	**1**	**0**	**1**	**1**	**1**	**2**	**3**	**A**	**8**
22	0	0	0	0	0	0	0	0	T	2
23	1	1	0	0	0	1	1	2	T	8
24	0	0	0	1	0	1	0	2	T	2
25	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**A**	**10**
26	1	1	0	0	0	0	1	1	T	12
27	1	1	1	1	1	1	3	3	T	4.8
28	1	1	0	0	1	0	2	1	T	3
29	0	1	0	0	1	0	1	1	T	2
30	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**A**	**9.2**
31	0	0	0	0	1	0	1	0	T	4.5
32	1	1	0	0	0	0	1	1	T	2
33	1	1	0	1	0	1	1	3	T	3

34	**1**	**1**	**0**	**0**	**0**	**1**	**1**	**2**	**A**	**12**
35	0	0	0	0	0	0	0	0	T	4
36	**1**	**1**	**0**	**0**	**0**	**1**	**1**	**2**	**A**	**6**
37	**1**	**0**	**0**	**0**	**1**	**0**	**2**	**0**	**A**	**7**
38	1	1	0	1	1	1	2	3	T	3
39	0	0	0	0	0	0	0	0	T	11.5
40	0	0	0	0	0	0	0	0	T	0.8
41	0	1	0	0	0	0	0	1	T	3.8
42	0	0	0	0	0	0	0	0	T	5
43	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**A**	**23**
44	0	0	0	0	0	0	0	0	T	1
45	**0**	**1**	**0**	**1**	**1**	**1**	**1**	**3**	**A**	**20**
46	0	0	1	1	1	1	2	2	T	6
47	1	1	0	1	0	1	1	3	T	2
48	**0**	**1**	**0**	**1**	**1**	**1**	**1**	**3**	**A**	**10**
49	1	1	0	1	0	1	1	3	T	2
50	**0**	**0**	**0**	**1**	**1**	**1**	**1**	**2**	**A**	**12**
51	1	1	1	1	0	1	2	3	T	5.8
52	**1**	**1**	**1**	**1**	**0**	**1**	**2**	**3**	**A**	**11.2**
53	**0**	**1**	**0**	**0**	**0**	**0**	**0**	**1**	**A**	**12**

54	**0**	**1**	**1**	**1**	**1**	**1**	**2**	**3**	**A**	**20**
55	1	1	0	1	0	1	1	3	T	9
56	1	1	1	1	0	1	2	3	T	8.8
57	1	1	0	0	0	0	1	1	T	1
58	1	1	0	0	0	0	1	1	T	4.5
59	**1**	**1**	**1**	**1**	**0**	**1**	**2**	**3**	**A**	**16.5**
60	1	1	0	0	0	0	1	1	T	2
61	0	0	0	0	0	0	0	0	T	5
62	1	1	0	0	0	0	1	1	T	7.6
63	1	1	0	0	0	0	1	1	T	9.8
64	1	0	0	0	0	0	1	0	T	2
65	**1**	**1**	**0**	**1**	**1**	**1**	**2**	**3**	**A**	**20**
66	1	1	0	1	1	1	2	3	T	3
67	1	1	0	1	0	0	1	2	T	10
68	1	1	0	0	0	0	1	1	T	3
69	1	1	0	1	0	1	1	3	T	1.3
70	0	0	0	0	0	0	0	0	T	2
71	1	1	0	0	0	1	1	2	T	3
72	1	1	0	0	0	0	1	1	T	2.8
73	0	0	0	0	0	1	0	1	T	7.5

74	**0**	**0**	**0**	**1**	**0**	**1**	**0**	**2**	**A**	**1**
75	1	1	0	1	1	1	2	3	T	3.2
76	1	1	0	0	1	0	2	1	T	4.4
77	**1**	**1**	**0**	**0**	**1**	**1**	**2**	**2**	**A**	**12.7**
78	1	1	0	0	0	0	1	1	T	4
79	1	0	0	0	0	0	1	0	T	2
80	0	0	0	0	0	0	0	0	T	1
81	1	1	0	1	0	1	1	3	T	4
82	0	1	0	0	0	0	0	1	T	2
83	1	1	0	0	1	0	2	1	T	2
84	**1**	**1**	**0**	**0**	**0**	**0**	**1**	**1**	**A**	**10.8**
85	1	1	0	1	0	1	1	3	T	1
86	1	1	0	0	0	0	1	1	T	4
87	0	0	0	0	0	0	0	0	T	1.3
88	1	1	0	1	0	1	1	3	T	3.2
89	1	1	0	0	0	0	1	1	T	4
90	0	0	0	0	0	0	0	0	T	2
91	1	1	0	1	0	1	1	3	T	3
92	1	1	1	1	1	1	3	3	T	4.2
93	0	0	0	1	0	1	0	2	T	2

94	**1**	**1**	**0**	**0**	**0**	**0**	**1**	**1**	**A**	**6**
95	**0**	**0**	**0**	**1**	**0**	**1**	**0**	**2**	**A**	**17.2**
96	1	1	0	0	0	0	1	1	T	11.4
97	**1**	**1**	**0**	**1**	**0**	**1**	**1**	**3**	**A**	**15**
98	**0**	**0**	**1**	**1**	**1**	**1**	**2**	**2**	**A**	**24**
99	0	0	0	0	0	0	0	0	T	6.5
100	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**A**	**1.4**
101	**1**	**1**	**0**	**1**	**1**	**1**	**2**	**3**	**A**	**9**
102	**1**	**1**	**0**	**0**	**0**	**0**	**1**	**1**	**A**	**15**
103	**0**	**1**	**0**	**0**	**0**	**0**	**0**	**1**	**A**	**4**
104	1	1	0	0	0	0	1	1	T	3.2
105	0	1	0	0	0	1	0	2	T	3.4
106	0	0	0	0	0	0	0	0	T	4.8
107	1	1	0	0	0	0	1	1	T	1
108	**1**	**1**	**0**	**0**	**0**	**0**	**1**	**1**	**A**	**7**
109	1	1	0	0	0	0	1	1	T	0.5
110	**1**	**1**	**0**	**0**	**0**	**0**	**1**	**1**	**A**	**10**
111	**1**	**1**	**0**	**0**	**0**	**0**	**1**	**1**	**A**	**23**
112	**1**	**1**	**0**	**1**	**1**	**1**	**2**	**3**	**A**	**15.8**
113	0	1	0	0	0	0	0	1	T	2

114	**0**	**1**	**0**	**0**	**0**	**1**	**0**	**2**	**A**	**9**
115	0	0	0	0	0	0	0	0	T	3.6
116	0	0	0	0	0	0	0	0	T	2
117	**1**	**1**	**0**	**0**	**0**	**0**	**1**	**1**	**A**	**5**
118	**1**	**1**	**0**	**0**	**0**	**1**	**1**	**2**	**A**	**19**
119	1	1	0	0	0	1	1	2	T	2
120	**1**	**1**	**0**	**0**	**0**	**0**	**1**	**1**	**A**	**14.5**
121	0	0	0	0	1	0	1	0	T	2
122	0	0	0	0	0	0	0	0	T	2.5
123	0	1	0	0	0	0	0	1	T	1
124	0	0	0	0	0	0	0	0	T	4
125	0	1	0	0	0	0	0	1	T	2
126	1	1	0	0	1	1	2	2	T	1.5
127	**0**	**0**	**0**	**0**	**1**	**1**	**1**	**1**	**A**	**8.5**

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Table showing clinical details of the 127 patients included in the study

Sl.No	NAME OF PATIENT	HOSPITAL NUMBER	BIOPSY NUMBER	SEX	AGE	WHO GRADE	LOCATION OF TUMOR	SIZE OF TUMOR	HISTOLOGICAL GRADE	MIB 1 -LI
1.	ajay kumar	646877c	14707/05	m	32	II	parietal	7x6x6	atypical	9%
2.	alam mridha	511961c	20300/04	m	34	II	parasagittal	4.5x3x4	atypical	15.10%
3.	amina begum	821855c	19271/06	f	48	I	right frontal	3x2.5		5.40%
4.	amir hossain	697141c	24223/05	m	48	I	parietal	5x3.5x3		1%
5.	amita rakshit	900614c	29009/06	f	56	I	frontal convexity	6X6x5.3	fibroblastic	1%
6.	anil mazumdar	841855c	17548/06	m	53	I	Intraventricular	3.5X4X4	metaplastic	11%
7.	Anju	030009d	15801/07	f	48	I	Planum sphenoidal	3.7x4x2.1	transitional	3%
8.	anupam ray	641070c	154489/05	m	38	II	parietal	4x3x3	atypical	10%
9.	Anusuya	005612c	11125/07	f	25	II	frontal convexity	4.5x6x7	atypical	8%
10.	Arup das	027920d	16635/07	m	31	I	parasagittal	3.5X3X2.7	psammomatous	2.80%
11.	ashwin kumar	506037c	24092/04	m	62	I	sphenoid wing	3.2x2.7x3.0		3%
12.	Asim Purkait	643540c	15246/05	m	42	I	parietal	5x4x3		6%
13.	aslam khan	712720c	26379/05	m	48	I	frontal	4.7x4		2%
14.	awadh bihari singh	490191c	23012/04	m	59	I	frontal convexity	3.5x3.5x3		2%
15.	Babul	979798c	12221/07	f	48	I	frontal convexity	5.2x2.1x4	angiomatous meningioma	3%
16.	badrunnessa	639263c	13159/05	f	44	I	parasagittal	6x6x6.5	transitional	5%
17.	bakkiyalakshmi	833696c	17666/06	f	64	I	petrous apex	3x4	secretory	4.80%
18.	bala rani banerjee	520820c	22585/04	f	59	II	olfactorygroove	4.9x5.2x5.3	atypical	8%
19.	bhola kora	682810c	20351/05	m	59	I	tentorial	4X4.5X4	meningothelial	2%
20.	bholanath raj bongshi	568767c	30813/04	m	42	II	parasagittal	3.4X4X3.5	clearcell	7%
21.	bimal bansriar	665928c	22109/05	m	67	II	parasagittal	3.5x4x5	atypical	8%

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22.	birendra gupta	690165c	22971/05	m	53	I	pterional	4.5x3.5x3	angiomatous	2%
23.	Brojen	004893d	10831/07	m	56	I	Falx	5.4X5.4X6		8.00%
24.	chabbi deb	823572c	16553/06	f	57	I	petrous	3.3 X 3.5	transitional	2%
25.	Chafiang aran	877448c	25426/06	f	37	II	tentorium	3.5x3.73.2	atypical	10%
26.	chaya ghosh	796667c	9554/06	m	46	I	parasagittal	2.5x3x2		12%
27.	chinmoyee	941561c	2647/07	f	51	I	basifrontal	5x3.2x3.5	secretory	4.80%
28.	depak dey	636728c	13670/05	m	44	I	frontal	5x4x5.6		3%
29.	dipak ranjan	057941c	17127/04	m	48	I	pterion	3x2.1x2.8		2%
30.	Drupada mondal	489892c	15511/04	m	48	II	parietal	5.0x4x3.5	atypical	9.20%
31.	farida akthar	809381c	11559/06	f	39	I	falcine	3x3.2x3.5		4.50%
32.	ferdoshi	617286c	10056/05	f	42	I	medial sphenoid wing	3.5x3.7x3	psamomatous	2%
33.	garata koteshwaramma	763499c	6586/06	f	45	I	Parasagittal	5x3.5x2.6		3.50%
34.	george	771572c	4052/06	m	58	II	Basifrontal	3.1x2.5x2.5	atypical	12%
35.	gita dawn	849312c	20007/06	f	61	I	petrous	2.5x2x2.5	psammomatous	4%
36.	haji mohammud azirruddin	796941c	9641/06	m	61	II	Falx	4.8x4x3.8	atypical	7%
37.	halima begum	738129c	31071/05	f	50	II	cerebellar convexity	5x5x	atypical	7%
38.	hari shankar misra	542011c	26271/04	m	35	I	falx	3.5x4.0x4.3		3%
39.	himanshu banerjee	446698c	15140/04	m	52	I	frontal convexity	1.3x1.6x2.6	microcystic	12%
40.	jabajeya thanka	524541c	29449/04	f	48	I	frontal convexity	3.5x3x3.5	transitional	0.80%
41.	Jagadish	016597d	17081/07	m	55	I	cpangle	5x5x4	fibroblastic	3.80%
42.	jagnath awon	579529c	1396/05	m	41	I	petroclival	4.5x4x3.5	transitional	5%
43.	jahar la chakraborty	604689c	6946/05	m	51	II	frontoparietal	2x2	atypical	23%

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44.	Jaya	020651d	17581/07	f	44	I	parasagittal	2.9x2.9x2.5		1%
45.	jharna das	891490c	28588/06	f	34	II	tentorial	4x4x4	atypical	20%
46.	josphine	812540c	13049/06	f	44	II	sphenoid wing	3.3X3X3	atypical	6%
47.	justin wheeler	854179c	22028/06	m	44	I	sphenoid wing	4x4x5.5	angiomatous	2%
48.	kajal begum	568000c	29793/04	f	41	II	frontal convexity	7x6x6	chordoid	10%
49.	kalidas	735315c	30829/05	m	54	I	olfactrory groove	4.5X3.4x3.9		2%
50.	kamala addya	830460c	15831/06	f	43	II	Parasagittal	6.5x5.7x5.0	atypical	12%
51.	Kanti	003778d	13104/07	f	35	I	frontal convexity	4.7x4.7x6	meningothelial	5.80%
52.	karuna mondal	487091c	16726/04	f	44	II	sphenoid wing	3.9x4.4x4.4	atypical	11.20%
53.	keshia devi	724356c	28655/05	f	63	II	Clinoidal	3X3X4		12%
54.	krishna mitra	610554c	7678/05	f	56	II	tentorial	6x5x7	atypical	20%
55.	Lal Mohan	957044C	1591/07	m	33	I	Tentorium	5x5.4x5		9%
56.	lalit mardi	602881c	7081/05	m	20	I	parietal	6x6x7	transitional	8.80%
57.	laxmi devi	525440c	24000/04	f	45	I	sphenoid wing	3x4x4.4	meningothelial	1%
58.	madan mohan	738342c	2240/06	m	62	I	parasagittal	3.9 x3.3x3.6		4.50%
59.	madhuri sharma	561760c	29796/04	f	40	II	pterional	4.3X4X5.2	atypical	16.50%
60.	mahamayamaity	653820c	16392/05	f	50	I	parasagittal	8x5x5		2%
61.	manas kumar	520319c	25267/04	m	41	I	Olfactorygroove	4x4x3		5%
62.	manira khatoon	511007c	25271/04	f	47	I	Olfactorygroove	3.5x3x3.5		7.60%
63.	manju devi	578099c	3481/05	f	41	II	planum sphenoidal	3.7X3.2X3.8	atypical	9.80%
64.	Manora	006256d	13100/07	f	44	I	frontal convexity	3.6x3.2x3	fibroblastic	2%
65.	Mary	991863c	7941/07	f	66	II	Parasagittal	7X4X4.2	clearcell	20%
66.	md golam rasu	657631c	17397/05	m	64	I	Tentorium	3x2x3		3%
67.	md.mozammmel haque	612073c	7845/05	m	53	II	Olfactorygroove	5.5x6x4.5	transitional	10%
68.	meena devi	679675c	22147/05	f	45	I	Planum sphenoidal	4.5x4.5x4		3%
69.	mhd abu said	454412c	13320/04	m	49	I	petroclival	4.7x4.1x3		1.30%
70.	mhd israil	457637c	12170/04	m	52	I	frontal convexity		microcystic	2%
71.	Mina	009455d	11533/07	f	28	I	tentorium	3x2.2x3.1	transitional	3%

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72.	mira sil	582696c	2440/05	f	47	I	parasagittal	4.5X4.4X4	transitional	2.80%
73.	mohammud attahullah khan	696360c	27962/05	m	10	II	Clinoidal	3x3.5x2.7	atypical	7.50%
74.	mohammud haurn khan	679170c	24530/05	m	52	II	parietal	3x4x2.5	transitional	1%
75.	Monir	022484d	15707/07	m	38	I	parasagittal	7.5x5x7	meningothelial	3.20%
76.	Mosammat	948623c	15478/07	f	36	I	frontal convexity	3x3.5x2	transitional	4.40%
77.	murari choudhari	582163c	1519/05	m	30	II	frontal convexity	5X4.5X4	chordoid	12.70%
78.	Murugan	971435c	13715/07	m	37	I	parietal	3x2.5x2.5	angiomatous meningioma	4%
79.	Namita	021839d	14259/07	f	50	I	parasagittal	7x7x6		2%
80.	narang	476159c	14233/04	f	38	I	petroclival	4.5x4x3.5		1%
81.	narayan chandra	229812c	10150/06	m	58	I	pterional	3.3X2.4x3.2	angiomatous	4%
82.	narayan mallya	563024c	5448/05	m	47	I	Tentorium	4.1x4x4.2	fibromatous	2%
83.	nayeema shad	536024c	26478/04	f	45	I	frontal	4.1x3x4.2		2%
84.	oheward laloo	838976c	17292/06	m	37	II	planum sphenoidal	6X5.6X5	atypical	10.80%
85.	om prakash	775964c	7541/06	m	31	I	parietal	5x3.4x4.3	microcystic	1%
86.	pankaj chakrabprty	807582c	13590/06	m	43	I	frontal convexity	3.8X3.4X3	transitional	4%
87.	prabir mukherjee	927700A	21372/04	m	53	I	tuberculum sellae	2x2x1.8		1.30%
88.	Pradip	017377d	13528/07	m	53	I	tuberculum sellae	7.3x7x3.5	meningothelial	3.20%
89.	pratima gorai	593540c	6410/05	f	42	I	atrium	3.0x3.6x3	transitional	4%
90.	r b singh	588146c	27960/05	m	49	I	frontal convexity	3.4X3.54.3		2%
91.	r.c.choudhary	660861c	18766/05	m	47	II	petroclaval	5x4x2		3%
92.	rafiqul anwar	566931c	658/05	m	48	I	parasagittal	4.2X3.4X2.5	transitional	4.20%
93.	ramapada	878074c	23898/06	m	22	I	sphenoid wing	5x2.5x3		2%
94.	ramgopal	635617c	13235/05	m	52	I	Clinoidal	3x3x3.5	transitional	6%

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95.	ranjan mr	587365c	5648/05	m	57	II	CP angle	5.3x 3.3x7	atypical	17.20%
96.	ratna rajbangshi	590956c	3544/05	m	51	I	parasagittal	3.7X3.5X4	transitional	11.40%
97.	Ratneswar	994635c	10526/07	m	54	II	parietal	3.5X4X2.5	atypical	15%
98.	ravi	040414B	26959/04	m	41	II	parietal	6x4.4x8	atypical	24%
99.	reba das	830380c	16149/06	f	68	I	parasagittal	6X6X6	fibroblastic	6.50%
100.	rezaul	619489c	10060/05	m	32	I	frontal convexity	5.4x6.4x6.7	atypical	1.40%
101.	rina guha	858722c	28702/06	f	48	I	sphenoid wing	4.8x3.8x4.3		9%
102.	sachindra dey	652928c	16284/05	m	64	II	ant cranial fossa	4x4x2	atypical	15%
103.	sandhya dey	497266c	23606/04	f	40	II	parietal	4x3.3x2	chordoid	4%
104.	sanjith rudra pal	851219c	20679/06	m	24	I	Falx	6x5.5X6	fibroblastic	3.20%
105.	sarbani banerjee	555136c	28910/04	f	61	I	frontal convexity	6.4x5..7x4.4	transitional	3.40%
106.	sefali dey	876529c	28120/06	f	58	II	planumsphenoidale	3.5x3.5x3		4.80%
107.	senowara begum	524240c	23008/04	f	50	I	parasagittal	4.2x4.9x4	microcystic	1%
108.	shaffrunnissa	775819c	5753/06	f	48	I	Clinoidal	4.5x4x4.8		7%
109.	shakuntala maji	530006c	25371/04	f	55	I	sphenoid wing	3x2.5x1.5		0.50%
110.	shambu narayan	775090c	5167/06	m	63	I	Planum spheoidale	4x4x5		10%
111.	shanmugam	487455c	17004/04	m	51	II	parietal	6x4.8x5	atypical	23%
112.	shiv kumari devi	554719c	29976/04	m	50	II	cavernous sinus	3.7X2.8X3	atypical	15.80%
113.	shova rani chatterjee	736065c	31216/05	f	54	I	planumsphenoidale	4.2x3x3		2%
114.	shyamali ghosh	761520c	6700/06	f	55	II	planumsphenoidale	3.8X3.4X3	atypical	9%
115.	sibeswarsha	854484c	20997/06	m	62	I	parietal	3X3	meningothelial	3.60%
116.	soma chattopadhyay	418996c	10838/05	f	33	I	parietal	2.2x2.8x2.6		2%
117.	Sumithra	038647d	17021/07	f	45	II	tentorium	2x1.5x2.5	atypical	5%
118.	sumitra rakhshit	476210c	14265/04	f	41	II	petroclival	5.8x5.3x5.5	atypical	19%
119.	sunitha	608868c	8259/05	f	22	I	frontal convexity	6.6x6.6x8	angiomatomatous	2%
120.	syed mhd arif	641869c	14424/05	m	39	II	falx	3.5x4x3	atypical	14.50%
121.	tabibur rahnman	694615c	23962/05	m	54	I	falx	7.4x4x5		2%

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122.	tahsin ali	566524c	30371/04	m	38	I	cerebellar	5X4.5X3	transitional	2.50%
123.	tapati basra	531873c	25763/04	f	42	I	falx	6x5x4.7	fibroblastic	1%
124.	tusar kanti maetya	727633c	15147/06	m	48	I	cpangle	4.4X4.3		4%
125.	Uma	985950C	9637/07	f	54	I	cpangle	3.3X4.2X5	fibroblastic	2%
126.	uttam pal	703263c	24812/05	m	38	I	frontal convexity	5x4x5	microcystic	1.50%
127.	vannamayil	772872c	23822/6	f	46	II	Tentorium	4X5x6	atypical	8.50%